ANALYSIS OF ALTERNATIVES

PUBLIC VERSION

Legal name of applicant(s): *Abbott Laboratories Limited*

Submitted by: *Abbott Laboratories Limited*

Substance: *4-(1,1,3,3-tetramethylbutyl) phenol, ethoxylated*

Use title: *Professional use as a surfactant in the final use of In-Vitro Diagnostic Devices (IVDs) for clinical testing using ARCHITECT, Alinity and ABBOTT PRISM automated analyser systems.*

Use number: *1*

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LIST OF ABBREVIATIONS

4-tert-OPnEO	4-(1,1,3,3-tetramethylbutyl) phenol, ethoxylated
AoA	Analysis of Alternatives
B	Bioaccumulative
BCF	Bioconcentration Factor
CAS	Chemical Abstracts Service
CLP	Classification, Labelling and Packaging
CMIA	Chemiluminescent Microparticle Immunoassay
CoRAP	Community Rolling Action Plan
CV	Coefficient of Variation
DNEL	Derived No-Effect Level
EEA	European Economic Area
EC	European Community
ECHA	European Chemical Agency
EU	European Union
GB	Great Britain, made up of England, Scotland, and Wales
HDL	High Density Lipoproteins
HIV	Human Immunodeficiency Virus
HLB	Hydrophile-Lipophile Balance
ISO	International Organization for Standardization
IVD	*In-Vitro* Diagnostic Device
IVDD	*In-Vitro* Diagnostic Device Directive
IVDR	*In-Vitro* Diagnostic Medical Device Regulation
kg	Kilogram
LAD	Latest Application Date
LDL	Low Density Lipoproteins
LD50	Lethal Dose 50
LoB	Limit of Blank
LoB/D/Q	Limit of Blank/Detection/Quantitation

LoD	Limit of Detection
LoQ	Limit of Quantitation
mg/kg bw/day	milligram/kilogram of bodyweight/day
mg/m^3	milligram/metre cubed
ml	Millilitre
mN/m	millinewton/metre
N/A	Not Applicable
NOEC	No Observed Effect Concentration
OP	Octylphenol
PACT	Public Activities Coordination Tool
PRIO	Swedish Chemicals Agency risk reduction tool
QSAR	Quantitative Structure–Activity Relationship
R&D	Research and Development
RAC / SEAC	Committees for Risk Assessment /Socio-Economic Analysis
REACH	Regulation (EC) 1907/2006 on Registration, Evaluation, Authorisation and Restriction of Chemicals
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Sunset Date
SVHC	Substances of Very High Concern
SEA	Socio-Economic Analysis
SIN	Substitute It Now
UVCB	Chemical Substances of Unknown or Variable Composition, Complex reaction products and Biological materials
vB	very Bioaccumulative
yr	Year

DECLARATION

The Applicant is aware of the fact that evidence might be requested to support information provided in this document.

We, Abbott Laboratories Limited, request that the information blanked out in the "public version" of the Analysis of Alternatives is not disclosed. We hereby declare that, to the best of our knowledge as of today, **30th September 2021,** the information is not publicly available, and in accordance with the due measures of protection that we have implemented, a member of the public should not be able to obtain access to this information without our consent or that of the third party whose commercial interests are at stake.

Signature: Date, Place:

Colleen O'Donnell

30 Sep 21, Sligo Ireland

Colleen O'Donnell
Program Director, Global Technical Operations
Abbott Ireland
Finisklin Business Park,
Sligo,
Ireland

1. SUMMARY

1.1 The Applicant

Abbott is a worldwide healthcare company. Abbott has a broad range of branded generic pharmaceuticals, medical devices, diagnostics, and nutrition products. The Company's diagnostics division, provides immunoassays, including blood screening products, and clinical chemistry tests. Its medical tests and diagnostic instrument systems are used worldwide by hospitals, laboratories and blood banks for clinical diagnosis and monitoring diseases. The diagnostics division manufactures a broad range of tests, including SARS-Cov-2, HIV, hepatitis, thyroid function, fertility and pregnancy, cardiology, renal and metabolic markers, therapeutic drug monitoring, detection of drugs of abuse and clinical chemistry assays and other indicators of health.

4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated, covering well-defined substances and UVCB substances, polymers and homologues (hereafter "4-tert-OPnEO" or "the substance") is used to produce In-Vitro Diagnostic Medical Devices, which are distributed by Abbott Diagnostics GmbH, a distribution center in Germany, for use by healthcare professionals in Great Britain (GB) and worldwide. Abbott Laboratories Limited is applying for an Authorisation for use by their customers.

As a result of the United Kingdom (UK) withdrawal from the European Union (EU) in 2021, (Abbott Laboratories Limited, hereinafter known as 'the Applicant') is now applying for an Authorisation for their Great Britain based customers under UK REACH. In the context of this Analysis of Alternatives (AoA), the Applicant includes the IVD kits as used by its customers based in Scotland, Wales and England (herein referred to as Great Britain or GB). As a result of the Northern Ireland (NI) Protocol, NI customers are not included as part of this application.

1.2 Uses and Function of 4-tert-OPnEO

The uses in the context of this Analysis of Alternatives (AoA) are for the downstream use of IVDs containing 4-tert-OPnEO by the Applicant's UK based customers:

> USE 1. Professional use as a surfactant in the final use of *In-Vitro* Diagnostic Devices (IVDs) for clinical testing using ARCHITECT, Alinity and ABBOTT PRISM automated analyser systems.

The substance is used in the end use of IVD reagents and test kits. 4-tert-OPnEO acts as an effective surfactant and wetting agent that reduces nonspecific interactions, prevents protein binding on surfaces and aggregation of proteins or microparticles. Furthermore, it promotes solubility and stabilises proteins, allowing for their detection.

This AoA documents the potential substitution of 4-tert-OPnEO in Use 1.

1.3 Identification of Possible Alternatives

Alternative technologies to the use of 4-tert-OPnEO in reagents of IVD products are not considered a viable option. Alternative technologies that do not depend on a surfactant such as 4-tert-OPnEO are not available with the breadth of menu and throughput required to meet the needs of the core laboratory and transfusion (blood screening) markets. Given that alternative technologies that could eliminate the need for 4-tert-OPnEO are not available, the Applicant has focused on the identification of an alternative surfactant that can fulfil the technical function of 4-tert-OPnEO within the IVD test kits.

Screening processes, elaborated in section 4, identified a number of potential alternatives. Initial screening criteria included chemical properties and recommendations from surfactant suppliers. A long list of 20 potential alternatives was generated using resources from R&D. Of the 20 long listed potential alternatives arising from the screening activities, 10 substances were identified as having potential to act as alternative in the formulation of IVD reagents. Further screening, based on key substance properties (Hydrophile-Lipophile Balance, hydrophobic tail structure, and cloud point), reduced the list to three potential alternatives that were identified as meeting the primary criteria for selection.

The screening analysis concluded that one alternative surfactant type, the secondary alcohol ethoxylates, have key substance properties that closely match those of 4-tert-OPnEO and may have the potential to act as an alternative to 4-tert-OPnEO for the use in IVDs. In addition, an overall reduction in risk to the environment would be achieved through this substitution. However, a determination of technical feasibility cannot be established until each individual impacted product completes design verification on each instrument system (ARCHITECT *i*, Alinity i, and Alinity s instruments).

1.4 Regulatory Requirements

Moreover, once the technical feasibility has been established, the substitution cannot be finalised until completion of lengthy external clinical performance evaluation studies and regulatory approval. The manufacture of IVDs reagents and test kits is regulated within the EU under the scope of the *In-Vitro* Diagnostic Directive (98/79/EC) IVDD) (which is in the process of being replaced by the *In-Vitro* Diagnostic Regulation (EU 2017/746) (IVDR) and compliance is fulfilled through a set of complimentary ISO Quality Standards. Stringent requirements for research and development and design verification activities to support regulatory approval of IVD product changes do not allow for swift substitution of 4-tert-OPnEO from the manufacturing processes. The EU IVDR did not take effect during the transition period and will not be transposed into law in Great Britain. Therefore, registrations are required for IVDs being placed on the market and any changes to products will meet the requirements for law in Great Britain.

The introduction of any change to the formulation of an IVD, reagent and test kit is subject to rigorous and lengthy internal quality procedures and external regulatory approval processes required to safeguard the health and safety of patients, users and other persons. This is achieved by ensuring that the manufacturers of IVDs follow specified procedures during design, manufacture and marketing. Thus, as explained in this AoA, the introduction of an alternative surfactant in the impacted IVDs requires a multitude of R&D and revalidation activities as well as global regulatory re-approvals.

1.5 The Requested Review Period

The process of finding a suitable alternative for substitution began in 2014. The Applicant has identified potential alternatives and commenced with establishment of technical feasibility. Where feasible, the Applicant is progressing products through the substitution and phase out process. The process of establishing technical feasibility for any given product involves a complex multi-step IVD manufacturing process. Due to physical capacity constraints within the laboratories and manufacturing facilities it is not possible to run technical feasibility studies on the approximately 200 IVD products in parallel. Moreover, studies have shown that the primary alternative is not technically feasible in some product applications, thus additional studies with secondary alternatives are required on a case by case basis.

Considering the need for the completion of internal validation of the alternatives within a large range of approximately 200 IVD products, the lengthy global regulatory approval timeframes combined with conversion periods for the Applicant's customers, substitution of the 4-tert-OPnEO from IVD reagents is not possible before the Sunset Date (SD). Consequently, the Applicant requests approval for a bridging Authorisation with a review period of 5.5 years (through 4-Jan-2028) for the Downstream Use of IVD reagents.

2. ANALYSIS OF SUBSTANCE FUNCTION

2.1 Annex XIV Substance Details

The substance was originally added onto Annex XIV of EU REACH (Authorisation list) [2] because it breaks down to 4-tert-Octylphenol that has endocrine disrupting properties for the environment. Annex XIV of EU REACH [1] was retained in UK REACH (The REACH etc. (Amendment etc.) (EU Exit) Regulations 2019; SI 2019 No. 758) with the same Latest Application Date (LAD) and Sunset Date (SD). In this instance the Applicant is able to benefit from transitional provisions introduced in The REACH etc. (Amendment etc.) (EU Exit) (No. 3) Regulations 2019; SI 2019 No. 1144, allowing for adjustment of the LAD and SD to 1st July 2022.

Table 1: Annex XIV substance details

Entry Number	Substance	Intrinsic properties	Latest Application Date	Sunset Date
42.	4-(1,1,3,3-Tetramethylbutyl) phenol, ethoxylated (covering well-defined substances and UVCB substances, polymers and homologues).	Endocrine disrupting properties (Article 57(f) - environment)	1th July 2022	1st July 2022

Abbott applied for authorisation to ECHA from its legal entities in Ireland and Germany prior to the Latest Application Date as per the EU REACH, with a final opinion by RAC/SEAC completed in December 2020. As a result of the UK exit from the EU, an authorisation package is required for GB. Therefore, this Analysis of Alternatives will focus on the impact on the GB downstream user only.

2.2 Aims and Scope of the Analysis of Alternatives

The aim of this AoA is to assess the potential alternatives and to demonstrate that no feasible alternatives to 4-tert-OPnEO will be available at the Sunset Date for the Applicant's *In-Vitro* Diagnostic Devices (IVDs). These IVDs are used by the Applicant's downstream users in GB. It also aims to describe the effort undertaken by the Applicant to find and implement a suitable alternative that is technically and economically feasible.

2.2.1 The Applicant

Abbott operates a dedicated distribution centre (Abbott Diagnostics GmbH) from where finished IVD kits are distributed to customers in GB and worldwide. Abbott applied for authorisation to ECHA from its legal entities in Ireland and Germany prior to the Latest Application Date as per the EU

REACH, with a final opinion by RAC/SEAC completed in December 2020, for the manufacturing in, and distribution from, its EU entities as well as on behalf of its EU customers, which are also considered Downstream Users of 4-tert-OPnEO contained within the IVDs.

As a result of the UK exit from the EU, customers in GB are considered Downstream Users of the substance within the IVD reagents and test kits. Abbott Laboratories Limited, hereafter "the Applicant", is applying for a bridging application for the downstream use of IVD reagents and test kits containing 4-tert-OPnEO on behalf of its GB customers.

2.2.2 The Applicant's products

The Applicant is applying for an Authorisation for its customers end use of Immunoassay and Clinical Chemistry IVD components using 4-tert-OPnEO in professional, clinical and laboratory settings (Use 1). The scope of the AoA covers approximately 200 products where the 4-tert-OPnEO must be substituted in a number of different components of the IVD kit. The Company's IVD business provides immunoassays, including blood screening products, and clinical chemistry tests. Its medical tests and diagnostic instrument systems are used worldwide by hospitals, laboratories and blood banks for clinical diagnosis and monitoring diseases. The Applicant manufactures a broad range of tests; including tests for SARS-CoV-2, HIV, hepatitis, thyroid function, fertility and pregnancy, cardiology, renal and metabolic markers, therapeutic drug monitoring, detection of drugs of abuse and clinical chemistry assays and other indicators of health. In 1985, the company developed the first licensed HIV blood screening test [3]. The functioning of the immunoassay and clinical chemistry IVD kits depends on the use of 4-tert-OPnEO in the IVD reagents.

2.2.3 IVD kits and regulatory information

The placing on the market and use of IVDs is regulated in the EU under Directive (EU) 98/79/EC on *in-vitro* diagnostic medical devices (IVDD) [4] which is being repealed and replaced by the *In-Vitro* Diagnostic Regulation (EU 2017/746) (IVDR) [5]. The regulation of IVDs aims to ensure that IVDs do not compromise the health and safety of patients, users and third parties and attain the performance levels specified by the manufacturer. As such, before a manufacturer can place an IVD product onto the EU market or make a change to an existing IVD product, it must meet a defined set of regulatory requirements and gain marketing approvals. The Applicant manufactures and supplies approximately 200 IVD products that would be required to complete regulatory approvals for any change resulting from the substitution of 4-tert-OPnEO. As such the Applicant must include the specific IVD regulatory requirements into their substitution plan for 4-tert-OPnEO. The EU IVDR did not take effect during the transition period and will not be transposed into law in Great Britain. Therefore, registrations are required for IVDs being placed on the market and any changes to products will meet the requirements for law in Great Britain.

During the review period for Professional use of IVD reagent kits, the Applicant will be substituting 4-tert-OPnEO from their products, where possible. At the same time, they will have to conform to the requirements of the IVDR and evaluate the products accordingly.

The IVDR regulation [5] defines an IVD in Article 2(2) as:

> *'in-vitro* diagnostic medical device' means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used *in-vitro* for the examination of specimens, including blood and tissue donations, derived from

> the human body, solely or principally for the purpose of providing information on one or more of the following;
>
> (a) concerning a physiological or pathological process or state;
> (b) concerning congenital physical or mental impairments;
> (c) concerning the predisposition to a medical condition or a disease;
> (d) to determine the safety and compatibility with potential recipients;
> (e) to predict treatment response or reactions;
> (f) to define or monitoring therapeutic measures.

The regulation further provides a definition of an IVD kit Article 2 (11):

> 'kit' means a set of components that are packaged together and intended to be used to perform a specific *in-vitro* diagnostic examination, or a part thereof;

Compliance with the regulatory requirements is fulfilled through a set of complimentary International Organization for Standardization (ISO) quality standards [6]. Compliance with the quality standards is mandatory for all manufacturers and the EU Regulation specifically addresses the safety, quality and performance of IVDs. The aim of the regulation is to ensure that IVDs do not compromise the health and safety of patients, users and third parties and attain the performance levels specified by the manufacturer.

IVD kit components produced by the Applicant include reagents, calibrators and controls which, in some cases, contain 4-tert-OPnEO. The IVD kit components are designed to be used in the Applicant's instrument systems which are essential for conducting a diagnostic test. The instrument systems are high throughput, fully automated analysers operated by trained professionals typically in clinical laboratories, hospitals, or blood banks and use two test techniques: **clinical chemistry** and **immunoassay**. Please refer to section 2.2.4 for a detailed description of the functional principle of these test techniques.

Abbott manufactures instrument systems that serve the Clinical Chemistry, Immunoassay Core Laboratory and Transfusion (blood screening) markets. The four different instrument systems in use in GB, the market segment served, and the test menu categories that utilise 4-tert-OPnEO are summarised in Appendix I. Figure 1 below is of the Applicant's Alinity analyser.

Figure 1: Alinity i automated analyser systems

The two main IVD test techniques used in the Applicant's instrument systems are clinical chemistry and immunoassay, described further in this section.

Reagent kits, calibrators, and controls are all required to perform an IVD assay test. 4-tert-OPnEO is used in the manufacture of reagents, calibrators, controls and as a constituent of their final formulation. 4-tert-OPnEO in IVD reagents acts as an effective surfactant and wetting agent that reduces nonspecific interactions, prevents protein binding on surfaces and aggregation of proteins or microparticles. Furthermore, it promotes solubility and stabilises proteins, allowing their detection. These functions, described in more detail in section 2.4.1, are key to the safe and effective performance of the IVD test kit.

An immunoassay reagent kit contains a minimum of two components; a solid phase or 'capture' component to bind the analyte in question, and a detection moiety. Paramagnetic microparticles are coated with a capture molecule (antigen, antibody, or viral particle) specific for the analyte being measured. The detection component is an acridinium-labelled conjugate that is used to generate the assay signal. An immunoassay reagent kit may also contain additional components, such as pre-treatment or assay specific diluents, depending on the analyte. The Applicant's immunoassay reagent kits are manufactured for use exclusively with the Applicant's own automated immunoassay instruments.

Clinical chemistry reagent kits are one or more cartridges that contain all of the necessary chemicals and/or enzymes needed to perform the analysis.

Calibrators are solutions with known values to establish the relationship between the amount of signal produced in the assay and the analyte concentration. Controls are samples that contain known concentrations of analyte. They are used to monitor the accuracy and precision performance of an assay and analyser.

2.2.4 Principles of IVD test techniques

A **clinical chemistry** test measures concentrations of biologically important ions (salts and minerals such as sodium and iron), small organic molecules (such as cholesterol, bilirubin, or certain substances of abuse), as well as large macromolecules (primarily enzymes or other proteins, such as lipases and lipoproteins (HDL or LDL)).

The Applicant's clinical chemistry tests are based on photometric detection which is the used by the instrument system to measure sample absorbance for the quantitation of analyte concentration. In performing the test, the instrument pipettes the reagents and the sample into a cuvette where a reaction takes place resulting in a change in absorbance. The instrument measures the change in absorbance which is proportional to the concentration of the analyte being measured.
4-tert-OPnEO in clinical chemistry reagents acts as an effective surfactant and wetting agent that reduces nonspecific interactions, prevents protein binding on surfaces and aggregation of proteins or microparticles. Furthermore, it promotes solubility and stabilises proteins, allowing their detection.

Potential alternatives to the use of 4-tert-OPnEO in clinical chemistry tests must fulfil these technical functions. In addition, potential alternatives must be chemically compatible with other reagent ingredients and must not interfere with either the maximal absorbance (end-point assays) or the rate of change in absorbance (rate assays).

An **immunoassay** is a test that uses antibody and antigen complexes as a means of generating a measurable result. The test utilises one or more selected antibodies and/or antigens to detect analytes of interest. The analytes being measured may be those that are naturally present in the body (such as

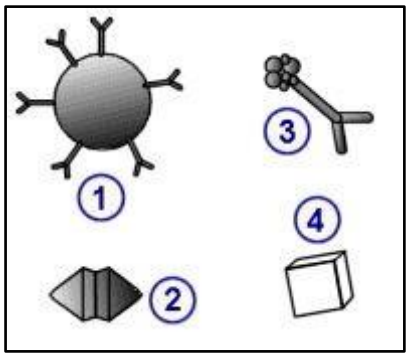
a thyroid hormone), those that the body produces but are not typically present (such as a cancer antigen), or those that do not naturally occur in the body (such as medication or a substance of abuse). Immunoassays can also detect viruses and/or the body's immune response to infection, serving as the basis for tests for the transfusion (blood screening) market.

4-tert-OPnEO use in immunoassay reagents acts as an effective surfactant and wetting agent that reduces nonspecific interactions, prevents protein binding on surfaces and aggregation of proteins or microparticles. Additionally, it promotes solubility and stabilises proteins, allowing their detection.

Potential alternatives to the use of 4-tert-OPnEO in immunoassay reagents must fulfil these technical functions. In addition, potential alternatives must be chemically compatible with other reagent ingredients and must not interfere with the immunoreaction between antibodies and antigens upon which the tests are based. Further details of the technical function of 4-tert-OPnEO and the technical feasibility criteria are discussed in section 4.2. The Applicant's immunoassay tests, dependent on surfactants based on 4-tert-OPnEO are based on the Chemiluminescent Microparticle Immunoassay (CMIA) technology. The reactants necessary for CMIA technology include:

- Paramagnetic microparticles coated with a capture molecule (antigen, antibody, or viral particle) specific for the analyte being measured.
- Acridinium-labelled conjugate.
- Pre-Trigger Solution and Trigger Solution.

The following graphic symbols are used to represent these reactants (Figure 2).



1. Anti-analyte microparticle with capture molecule
2. Sample analyte measured
3. Acridinium-labelled conjugate
4. Sample analyte not measured

Figure 2: CMIA reactants

A CMIA reaction sequence is the order of interactions between the analyte present in the sample and the reactants. A sequence is specific to the assay protocol. The following two-step reaction sequence illustrates the basic principles of a reaction

The specimen under test is introduced into the instrument system

1. The pipettor dispenses microparticles (paramagnetic microparticles coated with capture molecules) Figure 3, into the sample in the reaction vessel. The vortexer mixes the reaction mixture.

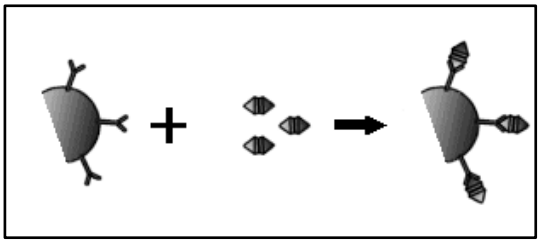


Figure 3: Sample and microparticle binding

2. The reaction mixture incubates, and the analyte present in the sample binds to the corresponding capture molecules on the microparticles forming the immune complex.
3. A magnet attracts the paramagnetic microparticles (bound to the specific analyte) to the wall of the reaction vessel. The wash zone manifold washes the reaction mixture to remove unbound materials.
4. The pipettor dispenses a chemiluminescent acridinium-labelled conjugate. The conjugate binds to the immune complex to complete the reaction mixture (Figure 4).

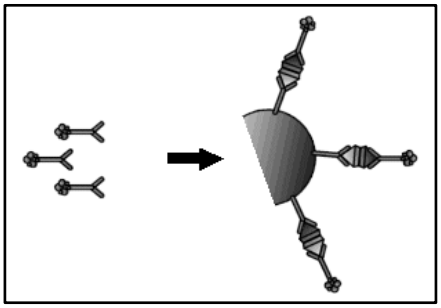


Figure 4: Addition of the acridinium-labelled conjugate

5. The reaction mixture incubates.

6. The wash zone manifold washes the reaction mixture to remove unbound materials.

7. The pre-trigger nozzle dispenses Pre-Trigger Solution (hydrogen peroxide) and the CMIA optical system takes a background read. Pre-Trigger performs the following functions:

    - Creates an acidic environment to prevent early release of energy (light emission).
    - Splits acridinium dye off the conjugate bound to the microparticle complex. This action prepares the acridinium dye for the next step.

8. The trigger nozzle dispenses Trigger Solution (sodium hydroxide) to the reaction mixture. The acridinium undergoes an oxidative reaction when exposed to peroxide and an alkaline solution. This reaction causes the chemiluminescent reaction to occur. N-methylacridone forms and releases energy (light emission) as it returns to its ground state.

9. The CMIA optical system measures the chemiluminescent signal (activated read) over a predefined time period to quantitate the analyte.

4-tert-OPnEO plays a key role in the optimal functioning of IVD reagents used in clinical laboratories for the detection and quantitation of biological markers and drugs contained in patient samples such as serum, plasma, whole blood, and urine [7]. Accuracy, precision, sensitivity and specificity are just a few of the essential product requirements for an IVD. The biological samples tested (e.g. serum, plasma, whole blood, and urine) are not homogeneous and contain a vast number of proteins and other biological agents that could interfere with the analysis.

To achieve this level of performance, the presence of 4-tert-OPnEO is required. Within the IVD, 4-tert-OPnEO acts by:

- reducing nonspecific interactions
- preventing protein binding on surfaces
- preventing aggregation of proteins or microparticles
- reducing bulk reagent surface tension
- promoting solubility and stabilising proteins allowing their detection

Reagents formulated using 4-tert-OPnEO function in this manner and have long been used as components of IVD reagents and test kits produced by the Applicant. Surfactant properties dictate interactions in and between the IVD reagents and other components of the system. These interactions in turn can have a profound impact on the final use of the IVD. The following product requirements are key performance indicators for IVD products.

- Precision: (minimal variation between measurements so that a single or duplicate result can be trusted, and results are consistent on different occasions). Surfactants enhance precision by improving solubility, preventing reagent loss to surfaces, enhancing the resuspension of the microparticle capture reagent, and modifying reagent rheology.

- Analytical & clinical sensitivity (quantitative measurement of minute concentrations of analyte, that is, analytical sensitivity may be expressed as the limit of detection, i.e. the smallest amount of the target marker that can be precisely detected and clinical sensitivity is the probability that the device gives a positive result in the presence of the target marker reducing non-specific binding will improve signal to noise ratio thus enhancing analyte detection. Additional modes in which a surfactant can impact sensitivity are:
  - as a solubilising agent: how effective is the surfactant in solubilising virus particles and other proteins to expose analyte for detection in infectious disease assays.
  - reducing non-specific background: reducing sample and signalling reagent hydrophobic interactions to latex microparticle surface will reduce non-specific binding.
  - reducing material adsorption to analytical system parts: In the absence of surfactant formulation, ingredients and sample components could interact adversely with analytical system parts (e.g. pipetting parts and reaction cells).

- Clinical specificity (clinical specificity is the probability of correctly classifying a result as negative when the true value indeed is negative): diagnostic samples may contain biological interferents that could lead to erroneous results. This can be reduced with optimised surfactant type and concentration.

- Shelf-life (Stability) (how long a product can be stored at recommended conditions and still meet product requirements upon use), surfactants can reduce unwanted excipient interactions, as formulation ingredients could interact adversely with each other to flocculate, precipitate, and hence reduce stability and/or reagent performance. Surfactants can improve water

solubility of hydrophobic reagents including acridinium conjugates, calibrators, controls, and microparticles during formulation, processing and storage.

- On-board stability (how long a product remains meeting product requirements while stored within the automated analyser):reducing material adsorption to primary packaging can reduce trending performance induced by changes in component concentrations during reagent storage and use while in the autoanalyser.

A potential alternative would be required to be proven to meet each of the above before any substitution effort could be envisaged. As such, these criteria form the basis of the R&D effort being undertaken by the Applicant.

2.2.5 Key substance properties required for technical function of 4-tert-OPnEO in the final IVD

To be considered a technically feasible potential alternative to the 4-tert-OPnEO in IVD reagents, a surfactant must be compatible with other ingredients in the formulation and must continue to provide its function without impacting the IVD's original design. IVD reagent kits are complex in nature [8], that is, they are made up of multiple components (e.g. microparticle capture reagent, conjugate detection/signalling reagent, assay and specimen diluents) all of which may contain 4-tert-OPnEO (See Appendix I Table II a-c). These components function together and in concert with the signal-generating system solutions (Pre-Trigger and Trigger). Given the complexity of the IVD reagent formulation and the interactions between components, the establishment of absolute design requirements for surfactant selection is an impractical expectation. In practice, surfactant selection for use in IVD reagents can be an empirical process [9] which recognises the complexity of reagent formulations, the multiple functions to be supported, and the historical individual product performance. Thus, when selecting a potential alternative to 4-tert-OPnEO, it is reasonable to choose one that is chemically similar and has similar physicochemical properties to maximise the probability that the alternative will function to support both the product requirements and its manufacturing processes in the same way as the 4-tert-OPnEO. Key properties are described below:

- Surfactant classification (anionic, cationic, amphoteric, non-ionic): This classification is based on the nature of the hydrophilic "tail" of the surfactant [8]. Antibody antigen interactions may involve ionic interactions. Charged surfactants such as the anionic, cationic, and amphoteric classes could perturb these interactions and have adverse effects.

- Hydrophile-lipophile balance number (HLB): For the non-ionic surfactants, this ratio relates the amount of chemical structure contributing to the surfactant hydrophilic and lipophilic portions. The HLB value can be predictive of how the surfactant interacts with the formulation[9]. The Applicant uses two 4-tert-OPnEO surfactants with HLB values of 13.5 and 17.6 respectively, depending on the reagents.

- Surface tension: Surfactants influence the interaction of diagnostic reagent formulations with surfaces. a [redacted]

- Cloud point: The cloud point of a non-ionic surfactant is the temperature where the mixture starts to phase separate with the surfactant forming its own structural phase. This behaviour is characteristic of non-ionic surfactants containing polyoxyethylene chains. A cloud point greater than 50°C would minimise the loss of surfactant activity that could occur due to exposure to elevated temperature during storage or shipment.

In summary, the Applicant considers the properties of 4-tert-OPnEO listed in Table 2 to be the most significant use of the surfactant in IVD reagents. Physicochemical properties are proposed to act as technical feasibility criteria for the identification and screening of potential alternatives in section 4.

Table 2 summaries the key substance properties and provides an overview of the inter-relationship between each property and product performance.

Table 2: Inter-relationship between key substance properties, technical function and product performance criteria

Technical function	**Assay component where function occurs**	**Key substance properties impacting function**	**Product requirement testing needed to verify technical function**
Reducing nonspecific interactions between capture (microparticle) and detection (conjugate) reagents	Microparticle Conjugate Assay Diluent	HLB Surface Tension	Precision Specificity Clinical Sensitivity Seroconversion LOB/D/Q Analytical Sensitivity Functional Sensitivity
Preventing protein binding on surfaces	Microparticle Conjugate Assay Diluent	HLB Surface tension	Precision Specificity Clinical Sensitivity Seroconversion LOB/D/Q Analytical Sensitivity Functional Sensitivity
Preventing aggregation of proteins	Microparticle Conjugate Assay Diluent Calibrators Controls	HLB	Shelf-life Stability Precision Specificity Clinical Sensitivity Seroconversion LOB/D/Q Analytical Sensitivity Functional Sensitivity
Preventing aggregation of microparticles	Microparticles	HLB	Shelf-life Stability On-board drift (microparticles) Precision Specificity Clinical Sensitivity Seroconversion LOB/D/Q Analytical Sensitivity Functional Sensitivity
Reducing bulk reagent surface tension (preventing ring formation)	Microparticles	Surface tension	On-board drift (microparticles)
Promoting solubility and stabilising proteins allowing their detection	Microparticle Conjugate Assay Diluent	HLB	Clinical Sensitivity Seroconversion

3. ANNUAL TONNAGE

3.1 Use 1 Annual Use Quantities

The use quantities for the Applicant's GB customers of IVD reagents are shown below in Table 3. The total cumulative annual use quantities for the Applicant's UK downstream customers is 0-1 tonnes/yr.

Assessed tonnage: 100 – 1000 (e) kg per year

The tonnage of OPnEO used by the Applicant's GB customers is calculated from the use quantity for the entire EEA (which includes the UK). The UK use quantity was initially calculated from the EEA downstream professional use quantity identified in the Applicant's EU REACH application 0167-02, which included customers in the UK. The use quantity was extracted based on the number of the Applicant's tests distributed in the UK, relative to that for the entire EEA. Number of tests is relevant as the EEA use quantity in the Applicant's EU REACH application was based on the average amount of 4-tert-OPnEO per test. The calculation used is as follows:

> Former EEA Use 2 tonnage X (UK #tests / Former EEA #tests) = e kg X (c) = 10-100 (e) kg

The GB use quantity was estimated from the UK use quantity calculated above. The conversion from UK to GB use quantity was made using an adjustment for the percentage of the Applicant's analysers (excluding ABBOTT PRISM quantities) that are used in GB vs total UK (b percent) which are not included in this assessment.

> GB use quantity = UK use quantity x (GB instrument placements / UK instrument placements) = e kg X (b) = 10-100 (e) kg

The GB value has been used for the exposure assessment in this document.

An additional 5-50 (e) kg is used in ABBOTT PRISM reagents, bringing the total ES1 quantity to 100 -1,000 (e) kg (GB). As a single GB customer is using the Applicant's ABBOTT PRISM analyser, the total amount of 4-tert-OPnEO was calculated using the number of kits forecast to be used by this customer through 2022, along with the amount of 4-tert-OPnEO contained within each product kit. ABBOTT PRISM instruments are not in use in Northern Ireland, therefore, this value is considered final for GB.

Table 3: Annual Quantities 4-tert-OPnEO (kg) by Downstream Users, Use 1

Year	Use 1 Reagent Releases (kg) prior to Sunset Date	Use 1 Reagent Releases (kg) after the Sunset Date	Pre-Trigger & Trigger Releases (kg) prior to Sunset Date	Total Downstream Releases (kg)
2021	93	0	192	286
2022	44	44	0	88
2023	0	81	0	81
2024	0	57	0	57
2025	0	21	0	21
2026	0	15	0	15
2027	0	10	0	10
2028	0	0	0	0

A representation of the anticipated reduction in use quantities through the requested review period, is provided in Figure 5.

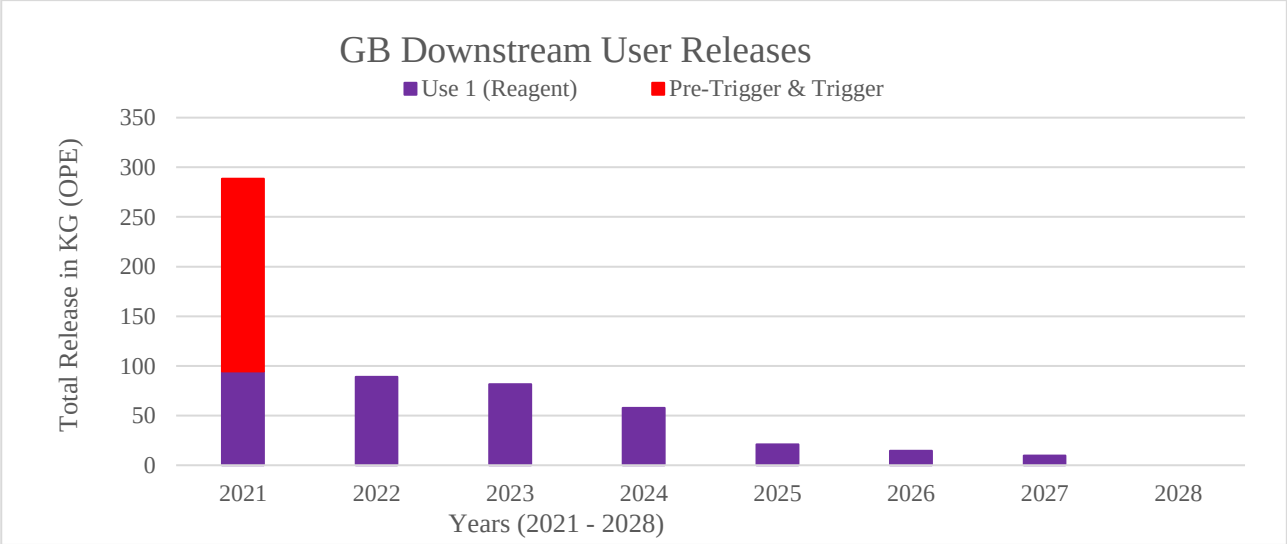


Figure 5: Use quantities reduction over the requested review period

4. IDENTIFICATION OF POSSIBLE ALTERNATIVES

The Applicant is committed to the removal of 4-tert-OPnEO from use in product manufacturing and subsequently from the final IVD kits used by professional users in a clinical setting. As such, preparatory work for the substitution of 4-tert-OPnEO began in 2014. The market for IVD testing is characterised by highly consolidated "core laboratories" that perform a wide variety of tests on highly automated and integrated clinical chemistry and immunoassay instrument systems. MedTech Europe [10], the European trade association representing the Diagnostics and Medical Devices manufacturers operating in Europe, surveyed industry members on the use and impact of a non-use scenario to the IVD supply in the EU. The 2018 survey found that 4-tert-OPnEO is used widely across all IVD categories and impacting all participating member companies. Therefore, it can be concluded that the

liquid reagents in the IVD test kits run on these instruments rely heavily on the use of 4-tert-OPnEO to fulfil the technical functions described above in section 2.4.1. Alternative technologies that do not depend on a surfactant such as 4-tert-OPnEO are not available with the breadth of menu and throughput required to meet the needs of the core laboratory market. The same can be said for the transfusion (blood screening) market which depends on high throughput automated analysers using liquid reagents that rely on 4-tert-OPnEO.

Given that alternative technologies that could eliminate the need for 4-tert-OPnEO are not available, the Applicant has focused its efforts, and this AoA on the identification of an alternative surfactant that can fulfil the technical function of 4-tert-OPnEO within the IVD test kits.

The substitution process involves a number of individual steps that mirror the Applicant's IVD design process, taking account of regulatory and technical performance requirements. The steps involved in the substitution project are given below and presented schematically in Figure 6. Elements of the process will be described in detail in the coming sections in so far as they relate to this AoA.

Steps of the Applicant's Substitution Process

1. Identification of Potential Alternatives Phase: Literature review for shortlisting primary and secondary potential alternatives.

2. Technical Feasibility Phase

a. Preliminary feasibility: Evaluation of performance of alternative in small batches of all assays requiring substitution.

b. Design verification: Manufacturing of full-scale lots and performing studies to verify that product requirements continue to be met.

3. External Clinical Performance Evaluation Phase: External studies carried out in a clinical setting, particularly for blood transfusion products

4. Regulatory Approval Phase: Submission of necessary documentation to regulatory authorities to receive marketing authorisation in all countries that the individual product is sold in.

5. Implementation Phase: Begin manufacture of new products without 4-tert-OPnEO to replace existing products on the market.

6. Customer Conversion Phase: Customers complete activities required to begin use of the product containing alternative in place of the product containing 4-tert-OPnEO.

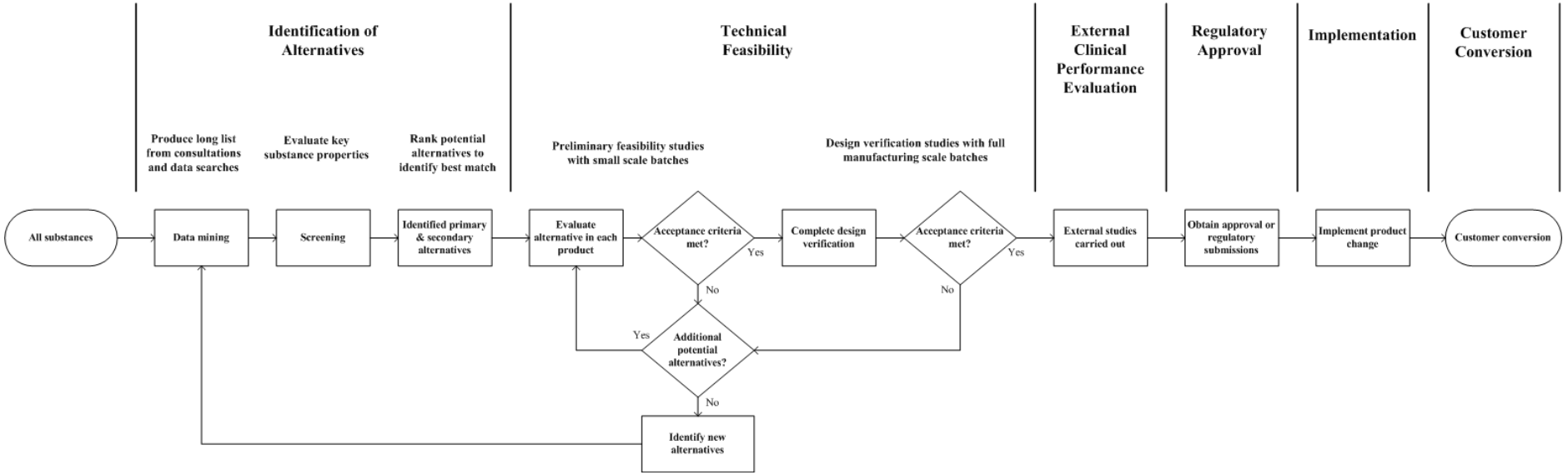


Figure 6: Applicant's substitution process

4.1 List of Possible Alternatives

The Applicant has made considerable progress in identifying suitable alternative surfactants to 4-tert-OPnEO for the formulation and use of IVD reagents. This section presents the identification and evaluation of potential alternatives, from screening through to shortlisting, for potential substitution of the 4-tert-OPnEO from IVD reagents.

4.2 Description of the Efforts Made to Identify Possible Alternatives

4.2.1 Data mining

During an initial data mining step, the Applicant carried out data searches and literature review, consulted supplier information on potential alternative surfactants to octylphenol ethoxylates described in section 4.2.8 of this AoA. A thorough internal consultation was also conducted to seek information on the experience of the use of different surfactant types. Experience within Abbott gained from the use of other surfactant types made a significant contribution to the identification process. From these activities a long list of 20 surfactant types was developed. Table 4 below lists the surfactant types identified.

Table 4: List of identified potential alternatives

Screening ID	Surfactant general description	CAS Number	Surfactant classification	Hydrophilic structure
1	secondary alcohol ethoxylate	68131-40-8 /84133-50-6	non-ionic	ethoxylate
2	polysorbate	9005-64-5/ 9005-65-6	non-ionic	ethoxylate
3	fatty alcohol ethoxylate	9002-92-0/3055-98-9	non-ionic	ethoxylate
4	trifunctional block copolymer surfactant	9003-11-6	non-ionic	ethoxylate
5	ethoxylated-propoxylated alcohol	64366-70-7	non-ionic	ethoxylate-propoxylate
6	branched secondary alcohol ethoxylates	60828-78-6	non-ionic	ethoxylate
7	tetra-functional block copolymer	26316-40-5	non-ionic	ethoxylate-propoxylate
8	ethoxylated acetylenic diols	9014-85-1	non-ionic	ethoxylate
9	tristyrylphenol ethoxylate	97734-09-05	non-ionic	ethoxylate
10	difunctional block copolymer	9003-11-06	non-ionic	ethoxylate
11	non-ionic, glycol chain based	69227-93-6	non-ionic	polysacharide based
12	polycyclic cholic acid based	86303-22-2	non-ionic	cholic acid based
13	natural surfactant	8047-15-2	non-ionic	glycoside with organic cyclic
14	sulfabetaine	14933-09-6	zwitterionic	ammonio propane sulfonate
15	non-detergent sulfobetaine	570412-84-9	zwitterionic	ammonio propane sulfonate
16	propane sulfonate, bile acid	75621-03-3	zwitterionic	cholic acid based
17	anionic surfactant	97-80-3	anionic	cocoyl glycinate
18	bile acid	73163-53-8	ionic	cholic acid based
19	lauryl sulfate	151-21-3	ionic	sulphate head
20	quaternary ammonium surfactant	57-09-0	ionic	ammonium head

The screening and initial assessment of technical feasibility of potential alternatives was based on a stepwise approach that screened potential alternatives based on key substance properties as outlined in section 2.4.1. The process is presented schematically below (Figure 7).

There are several advantages to this approach. First, the probability of functional matching through chemical similarity is increased while ensuring the potential alternatives have eliminated the concern for the environment. This would also allow the Applicant to reduce the number of potential alternatives to those with the greatest potential of producing acceptable results.

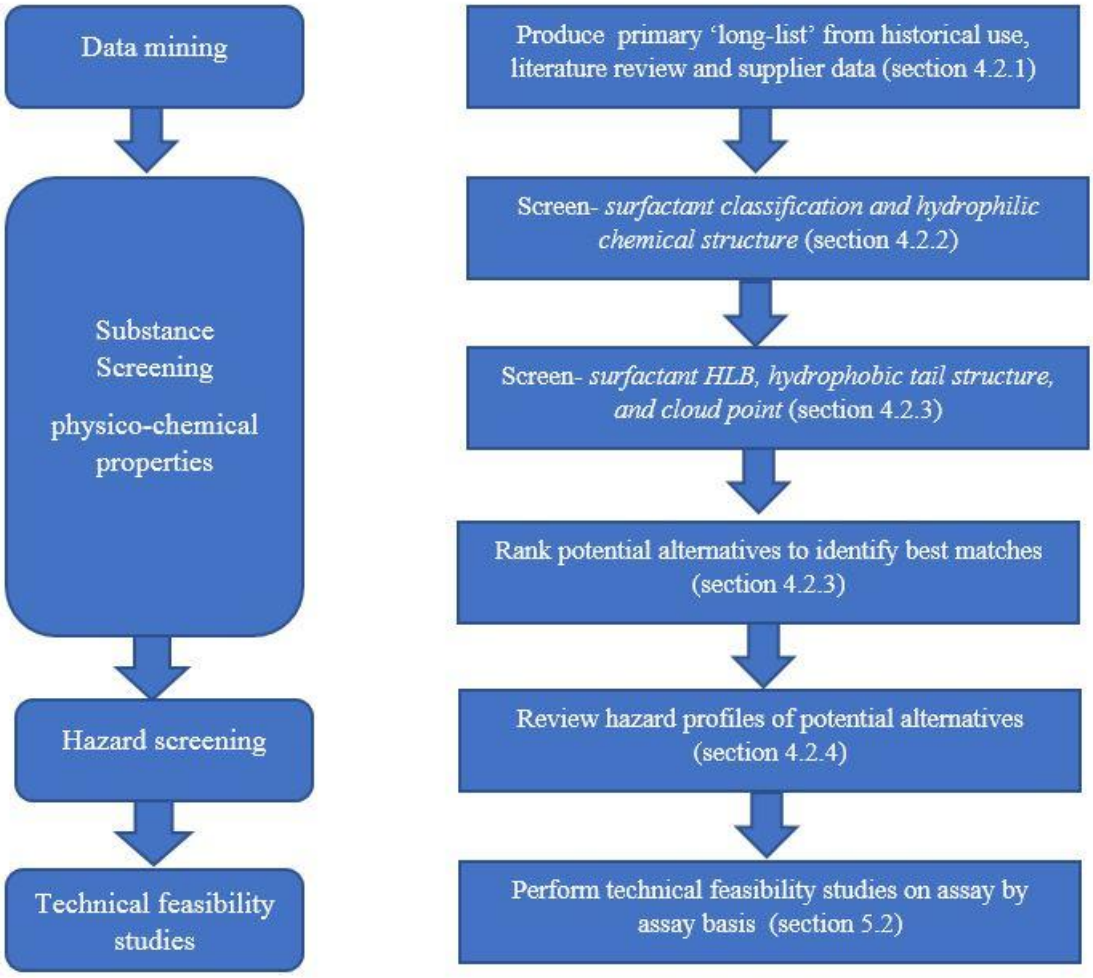


Figure 7: Identification of potential alternatives - Stepwise approach

4.2.2 Screening based on surfactant classification and hydrophilic chemical structure

Surfactants containing 4-tert-OPnEOs are non-ionic, thus non-ionic surfactants were the primary target category in the screening process. Furthermore, because the non-ionic surfactants currently used by the Applicant are of the ethoxylated nature, targeting ethoxylated surfactants ensured best chemical matching to the current surfactant in use.

Of the 20 surfactant types, 10 surfactants were deemed to meet step 1 criteria, i.e. these surfactant types were both non-ionic and ethoxylated. The remaining 10 surfactant types at the bottom of Table 5, were deemed not to meet either one or both properties required to satisfy the technical functions of 4-tert-OPnEO and were removed from consideration for further assessment.

Table 5: Long-list of surfactants considered for screening based on surfactant classification and hydrophilic structure

Screening ID	Surfactant general description	CAS Number	Surfactant classification	Hydrophilic structure
1	secondary alcohol ethoxylate	68131-40-8 /84133-50-6	non-ionic	ethoxylate
2	polysorbate	9005-64-5/9005-65-6	non-ionic	ethoxylate
3	fatty alcohol ethoxylate	9002-92-0/3055-98-9	non-ionic	ethoxylate
4	trifunctional block copolymer surfactant	9003-11-6	non-ionic	ethoxylate
5	ethoxylated-propoxylated alcohol	64366-70-7	non-ionic	ethoxylate-propoxylate
6	branched secondary alcohol ethoxylates	60828-78-6	non-ionic	ethoxylate
7	tetra-functional block copolymer	26316-40-5	non-ionic	ethoxylate-propoxylate
8	ethoxylated acetylenic diols	9014-85-1	non-ionic	ethoxylate
9	tristyrylphenol ethoxylate	97734-09-05	non-ionic	ethoxylate
10	difunctional block copolymer	9003-11-06	non-ionic	ethoxylate
11	non-ionic, glycol chain based	69227-93-6	non-ionic	polysaccharide based
12	polycyclic cholic acid based	86303-22-2	non-ionic	cholic acid based
13	natural surfactant	8047-15-2	non-ionic	glycoside with organic cyclic structures
14	sulfabetaine	14933-09-6	zwitterionic	ammonio propane sulfonate
15	non-detergent sulfobetaine	570412-84-9	zwitterionic	ammonio propane sulfonate
16	propane sulfonate, bile acid	75621-03-3	zwitterionic	cholic acid based
17	anionic surfactant	97-80-3	anionic	cocoyl glycinate
18	bile acid	73163-53-8	ionic	cholic acid based
19	lauryl sulfate	151-21-3	ionic	sulphate head
20	quaternary ammonium surfactant	57-09-0	ionic	ammonium head

4.2.3 Screening based on HLB, hydrophobic tail, and cloud point

From the 10 possible alternative surfactant types listed in Table 5, 16 individual non-ionic and polyethoxylated surfactants were evaluated further with focus on the hydrophobic structure and its contribution to surfactant properties. While the range of acceptable HLB values may vary from application to application [9], choosing an alternative with HLB comparable to that of 4-tert-OPnEO

is expected to increase the probability that the alternative will be suitable. For this reason, it is practical to define a range of targeted HLB values. The Applicant uses two surfactants containing 4-tert-OPnEO with HLB reported values of 13.5 and 17.6. A range of HLB values between 10 to 20 was therefore considered to be an acceptable starting point for possible alternatives.

In addition to the HLB value, potential alternatives were screened based on the complexity of the hydrophobic tail which has been reported to impact the rate of biodegradation [11]. Therefore, surfactants with simple linear aliphatic structures were selected over surfactants with branched or more complex structures with potentially slower rate of biodegradation. Finally, the Applicant opted to select surfactants that would not easily phase out of solution due to warm temperatures (i.e. cloud point >50°C) as the Applicant's products are often shipped ambient and must sustain temperature stability challenges. The intent was to simplify the execution of the technical feasibility studies as testing several surfactants would be lengthy due to the number of impacted products. Selecting the best chemical matching would provide a primary alternative option that could be tested against technical feasibility and support the outlined surfactant screening process. The results of this second screening step are summarised in Table 6.

Table 6: Surfactant screening list based on HLB, hydrophobic tail, and cloud point

ID	HLB	Hydrophobic tail	Cloud point °C >50 °C	Decision
1a	13.3	Linear aliphatic chain	60	Move forward
1b	18.0	Linear aliphatic chain	76	Move forward
2a	15.0	Linear aliphatic chain	65	Move forward
2b	16.7	Linear aliphatic chain	76	Move forward
3a	13.1	Linear aliphatic chain	None available	Move forward
3b	16.9	Linear aliphatic chain	>100	Move forward
4	18-23	Propylene oxide	65	Do not move forward: HLB too far away
5	12.5	Propylene oxide and branched aliphatic chain	61	Do not move forward: branched aliphatic chain
6a	13.1	Branched aliphatic chain	36	Do not move forward: low cloud point and branched aliphatic chain
6b	14.0	Branched aliphatic chain	65	Do not move forward: branched aliphatic chain
6c	14.4	Branched aliphatic chain	76	Do not move forward: branched aliphatic chain
7a	24.0	Propylene oxide	>100	Do not move forward: HLB too far away
7b	24.0	Propylene oxide	>100	Do not move forward: HLB too far away
8	13.0	Branched aliphatic chain	63	Do not move forward: branched aliphatic chain
9	13.0	Polystyrylphenol	62	Do not move forward: complex hydrophobic tail
10	12.0	Propylene oxide	46	Do not move forward: low cloud point

From the last screening step, three potential alternative surfactant types (represented by two individual surfactants each), presented in Table 8 were identified based on HLB, hydrophobic tail structure, and cloud point. Potential alternatives with branched hydrophobic tails were eliminated as were alternatives deemed to have HLB and/or cloud point that were too far away from those of 4-tert-OPnEO. A comparison of the final three alternatives with 4-tert-OPnEO of the key substance properties, HLB and surface tension and final ranking of the alternatives is presented in Table 7.

Table 7: Highest ranked potential alternatives after screening

Original screening ID	Surfactant type	Final ranking	HLB	Surface tension
a	Octylphenol ethoxylate (4-tert-OPnEO)	N/A existing surfactant	13.5	33
1a	Secondary alcohol ethoxylate	1	13.3	30
b	Octylphenol ethoxylate (4-tert-OPnEO)	N/A existing surfactant	17.6	52
1b	Secondary alcohol ethoxylate	1	18.0	45
2a	Polysorbate	2	15.0	38
2b	Polysorbate	2	16.7	39.6
3a	Fatty alcohol ethoxylate	3	13.1	34
3b	Fatty alcohol ethoxylate	3	16.9	43

Alternative 1 (a&b). Secondary alcohol ethoxylates have key substance properties (HLB, surface tension) that most closely match those of the two octylphenol ethoxylates used by the Applicant and are the primary short-listed alternative. In addition to possessing key substance properties that closely match the two octylphenol ethoxylates in use, the Applicant has some experience with use of the secondary alcohol ethoxylates in other products on the market and in development which contributes to their selection as the primary alternative.

Alternative 2 (a&b). Polysorbates are also currently used in some of the Applicant's reagent formulations. Key substance properties do not match those of the existing 4-tert-OPnEO surfactants as closely as the secondary alcohol ethoxylates. Polysorbates contain a labile ester bond in the chemical structure that can undergo hydrolysis in some reagent formulations with subsequent loss of surfactant activity.

Alternative 3 (a&b). Fatty alcohol ethoxylates are also currently used in some of the Applicant's reagent formulations. Key substance properties do not match those of the existing 4-tert-OPnEO surfactants as closely as the secondary alcohol ethoxylates. In the Applicant's experience, the fatty alcohol ethoxylate can be difficult to handle as they may be in a solid state at room temperature; commercially available solutions are sometimes highly viscous and gel-like making for difficult handling during formulation.

4.2.4 Hazard screening of potential alternatives

The hazard classifications of potential alternatives were reviewed using information from the ECHA public dissemination site [12] and from suppliers Safety Data Sheet [13].Table 8 below summarises the available data on the substances. The three surfactant types assessed below were considered to have desirable intrinsic properties to warrant their choice for further assessment. A complete hazard

assessment of the Alternative No.1 (a&b) (secondary alcohol ethoxylate) is presented in section 5.4 of this AoA.

Table 8: Alternatives hazard screening

Surfactant ID	CAS Number	Hazard classification	Conclusion
1 (a&b) Secondary alcohol ethoxylate	68131-40-8 /84133-50-6	Aquatic Chronic Cat 3 H412: Harmful to aquatic life with long lasting effects [15].	Suitable to proceed with technical feasibility testing Reduction of overall risk due to transition to the alternative
2 (a&b) Polysorbates	9005-64-5 /9005-65-6	Not classified [12]	Suitable to proceed with technical feasibility testing Reduction of overall risk due to transition to the alternative
3 (a&b) Fatty alcohol ethoxylate	9002-92-0 /3055-98-9	H302: Harmful if swallowed. H319: Causes serious eye irritation. [13]	Suitable to proceed with technical feasibility testing Reduction of overall risk due to transition to the alternative
Source(s): [12], [13], [15]			

4.2.5 Summary and conclusion of potential alternative screening and selection process

In summary, screening of 20 potential alternatives using substance physicochemical properties and chemical structure identified three surfactant types that could potentially act as an alternative for 4-tert OPnEO in IVDs. Furthermore, these three surfactant types are not considered to have hazardous properties that would impact their selection for future use in line with the Applicant's policies on substitution. Considering the key substance, stability considerations and handling properties of the three potential alternatives, the secondary alcohol ethoxylates Alternative No. 1 (a&b) was selected as the final primary short-listed alternative for further R&D studies.

4.2.6 Research and development

Abbott has a dedicated diagnostics research organisation with more than 40 years of experience in the development of IVD products. The Diluent Research and Formulations Group has specific expertise in development and optimisation of reagent formulations and of the critical role that surfactants such as 4-tert-OPnEO play in IVD product performance. Initial evaluation of the use of secondary alcohol ethoxylates as a substitute for 4-tert-OPnEO in IVD reagent formulations began in 2014. Ongoing research on diluent formulation provides the scientific support to the identification of possible alternatives.

4.2.7 Substitution effort taken by the Applicant if an authorisation is granted

As described previously, the Applicant has identified a primary potential alternative for 4-tert-OPnEO use in IVDs reagents. A comprehensive substitution and phase-out program has been developed and is currently underway to establish technical feasibility, external clinical performance, and regulatory approvals for all the Applicant's impacted products. With approximately 200 products undergoing substitution , the overall timeline is expected to take approximately 14 years from start of research to the end of substitution, to convert all products away from 4-tert-OPnEO. Substitution activities were initiated in 2014, upon funding approval, laboratory set up, and resourcing, with activities expected to continue through to the end of 2027. The ABBOTT PRISM system is in the process of being

replaced by the Alinity s system. The ABBOTT PRISM reagents utilising 4-tert-OPnEO are expected to be discontinued during the review period, therefore, substitution efforts will be focused on the reagents associated with the Alinity s system. The timeline required to complete substitution and phase out for all of the Applicant's products is shown below in Figure 8.

Figure 8: Projected timeline for the substitution of 4-tert-OPnEO from the Applicant's IVD reagents.

- **4.2.7.1 Description of the substitution and phase-out plan**

1. Identification of Alternatives Phase

As described previously in section 4.1, possible alternatives were identified via a literature search, consultation with suppliers and with internal departments. Further characterisation was performed to determine surfactants that were likely to be technically feasible as an alternative to 4-tert-OPnEO based on their chemical structure and physical-chemical properties. Once the primary alternative was identified, the evaluation moved to the next phase. Identification of potential alternatives was completed in 2014.

2. Technical Feasibility Phase

(a) Preliminary Feasibility: During this phase, each product impacted by substitution is manufactured at a small scale with side-by-side batches containing either 4-tert-OPnEO or the primary alternative. The assay performance of the manufactured product is then evaluated using studies described in section 5.2. Comparative performance studies are conducted between the product manufactured with 4-tert-OPnEO and the product manufactured with the identified alternative. Where results are favourable, the product moves to the next phase for additional and more thorough evaluation. Where results are not favourable, the product requires additional characterisation to determine whether an alternative concentration or alternative substance will provide the required assay performance**.** Preliminary technical feasibility activities began in 2015 and were completed in 2021.

(b) Design Verification: Completion of preliminary technical feasibility studies for some products in 2017 and 2018 allowed the Applicant to shift resources to begin the Design Verification Phase in 2018. At this stage, full scale production lots of the product are manufactured with the alternative substance. This requires drafting the production documents to manufacture the required number of verification lots. In addition, subject matter experts with in-depth knowledge of individual products are needed to draft and approve protocols required to complete the design verification product requirement testing outlined in section

5.2. Design verification testing is completed to verify that product manufactured with the alternative substance meets all product requirements and continues to perform in an equivalent manner to product manufactured with 4-tert-OPnEO. Highly skilled technical resources are also needed for verification and report creation as well as review and approval of the design verification reports. The entire activity is carried out under a strictly controlled design planning process dictated by regulatory requirements for IVDs. The Applicant's experience with similar product changes indicates that this design process requires a minimum of 18 months for a single product to complete. At this stage, if a product shows unacceptable performance, it will return to the preliminary feasibility phase to determine changes required to produce a product meeting the product specifications. As discussed further below, it is not technically nor logistically feasible to run all products through the design verification phase in parallel. Products made by third party manufacturers will be substituted in the same time period. Design verification activities are scheduled through 2025.

3. *External Clinical Performance Evaluation Phase*:

For some products, particularly blood screening products, a requirement exists to perform external studies in a clinical setting. This entails the instruments for the impacted products are either installed or are present in a customer laboratory. The number of specimens requiring testing can exceed 5,000 for many of the impacted products. External studies are scheduled from 2021 through 2025.

4. Regulatory Approval Phase:

Once the product has completed design verification studies, and, if required, external clinical performance evaluation and is thereby shown to meet the product requirements, the regulatory documentation is drafted. As these products are *in-vitro* medical devices, they require approval from regulatory bodies to ensure the conformity of the product with the relevant quality, safety and efficacy regulations. Extensive documentation is required to be compiled on each product and submitted to multiple regulatory agencies across the world. Review times in the various countries can be extensive, with some countries requiring up to 18 months to review a package. Once approval is obtained from all the impacted countries, the alternative substance can be implemented into the manufacturing process for commercial use. Products beginning design verification studies in 2018 are scheduled to begin the Regulatory Approval Phase in 2020. The last regulatory approvals for products completing Design verification and external clinical Performance Evaluation activities at later dates are expected to be received in 2026.

5. Implementation phase:

In this phase, the documents drafted in the Design Verification Phase replace the current documents for manufacturing the product with new product labelling ordered if required. The first lots to stock utilising the alternative surfactant will be manufactured and readied for distribution. Final lots using 4-tert-OPnEO substance will be manufactured to allow time for customers to convert to the new formulation. Changes are then made to the impacted recipes, so that products are manufactured using the identified alternative. Once the production documents have been updated, any new lots of a product will no longer contain 4-tert-OPnEO**.** The Implementation Phase is scheduled to begin in 2022 and run into 2026.

6. Customer Conversion phase:

In the final phase, the product is distributed to customers for use in laboratories generating patient results. The current distributed products have expiration dates up to 18 months, therefore, a period of time is needed to convert all customers from the products containing the 4-tert-OPnEO to those

containing the substituted substance. Based on evaluation of customer ordering patterns, it has been identified that the conversion is expected to occur in approximately 6 months, once the product begins shipping to downstream users (customers). In rare cases, additional time may be required for customers to perform cross-over testing studies, as required by individual laboratory procedures. Cross-over testing studies are performed by downstream users to demonstrate equivalency of results obtained before and after the product change. Such studies may be warranted if internal design verification and/or validation studies identify a higher than expected bias with the new formulation. An example would be studies performed as required, to confirm and/or establish the laboratory's quality control ranges, or normal ranges for patient results. Once a customer has begun utilising the product containing the alternative, they will no longer be able to source the product containing 4-tert-OPnEO. The Applicant has a formal process for customer communication consisting of Technical Bulletins and Customer Letters that will be used during Customer Conversion to inform the downstream users of the substitution and any actions required for implementation. Customer conversion for products beginning design verification activities in 2018 is expected to be completed in 2021; the last customer conversions for products completing Implementation at later dates are expected to occur by 2027.

An example timeline for a single product is provided below (Figure 9):

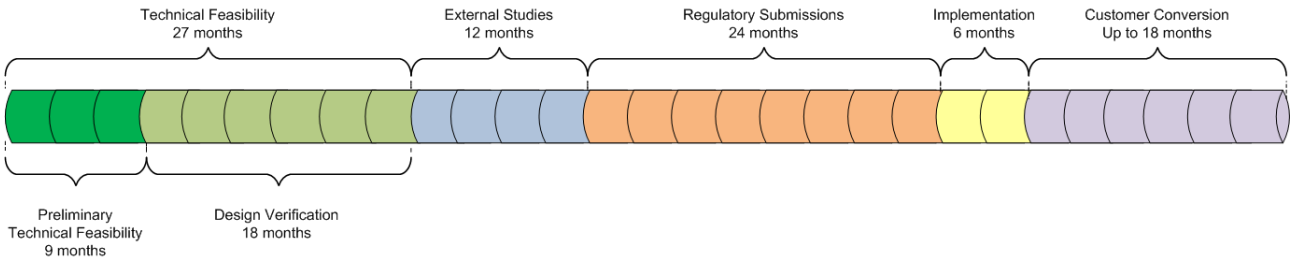


Figure 9: Timeline for substitution of 4-tert-OPnEO from a single product

4.2.7.2 Constraints and dependencies impacting substitution in IVD reagents

The Applicant is currently within the Technical Feasibility Phase of its substitution process. As each product has a specific, individual chemistry and formulation, each product needs to complete the entire process as outlined above before substitution is completed. The Applicant has approximately 200 IVD products impacted by substitution, each of which needs to undergo the above process. Constraints in the physical manufacturing plant and instrument testing lab capacity make it impossible to run design verification on all products in parallel.

Production of verification lots: While the reagent formulation can be completed in a matter of days, production of design verification lots entails the entire multi-step IVD kit manufacturing process starting with antigen production and purification, diluent formulation, microparticle coating, conjugation, blending and bulking, filling and kit pack. The cycle time from start to finish can take several months.

Regulatory Approvals / IVDR: Timely regulatory approval is a critical factor for establishing availability of alternatives and therefore adherence to the substitution plan. With the implementation date of the IVDR coinciding with the substitution timing, synergies have been identified between the IVDR submissions and the 4-tert-OPnEO substitution, allowing the regulatory submissions to be performed together.

The ABBOTT PRISM system is in the process of being replaced by the Alinity s System. The reagents utilising 4-tert-OPnEO are expected to be discontinued during the review period, therefore, substitution efforts will be focused on the reagents associated with the Alinity s system.

Therefore, the Applicant is seeking a 5.5 year review period to allow for the complete substitution and for products containing 4-tert-OPnEO to be consumed by customers or to reach their expiry.

4.2.8 Data searches

The Applicant carried out data searches using online resources and internal consultations for the alternative selection and screening process under the following headings;

1. Identification of potential alternatives
For the identification of possible alternatives, the Applicant performed an online search for "Octylphenol ethoxylates-alternatives" and used the information available from a major producer of 4-tert-OPnEO. The producer offers specific guidance on the alternatives to the octylphenol ethoxylates across a large number of different applications.

Guidance document title: **Alternatives to Alkyl Phenol Ethoxylate (APE, APEO) Surfactants**

Available from http://msdssearch.dow.com/

This document was used as a starting point for the generation of the initial list of potential alternatives to 4-tert-OPnEO.

2. Screening of alternatives
For the specific information on screening potential alternatives using physical-chemical properties, the Applicant consulted the following data sources.

Suppliers' SDS library: Available from www.sigmaaldrich.com/
ECHA dissemination site for registration information from www.echa.europa.eu/information-on-chemicals

3. Hazard assessment of alternatives
For the screening and hazard assessment of the shortlisted alternatives, the following public online resources were consulted;

- ECHA dissemination site, classification and labelling and registration information https://echa.europa.eu/information-on-chemicals
- SIN list by ChemSec https://chemsec.org/sin-list/
- Swedish Chemicals Agency PRIO database https://www.kemi.se/en/prio-start/search-in-the-database
- Swedish Chemicals Agency Restricted Substances Database https://webapps.kemi.se/begransningsdatabasen/Sok.aspx
- Yordas Hive https://www.yordasgroup.com/hive/

The Applicant will expand on these data searches as needed should the currently identified potential alternatives be not technically feasible in any applications.

4.2.9 Consultations

Subject matter experts in various departments of the company were consulted during the data mining phase of the alternative selection process. Surfactant manufacturer literature on alternatives to 4-tert-OPnEO was also consulted which led to the identification of the secondary alcohol ethoxylates.

The Applicant will expand on these consultations as needed should the currently identified potential alternatives be not technically feasible in any applications.

5. SUITABILITY AND AVAILABILITY OF POSSIBLE ALTERNATIVES

The alternative surfactants, which demonstrated the greatest potential for successful substitution, are described in the following sections of this AoA. This assessment aims to identify the best option for substitution, taking account of the technical feasibility, economic viability, potential for risk reduction and the availability of the substance for substitution.

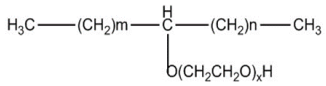
The Applicant must substitute 4-tert-OPnEO from reagents impacting approximately 200 different assay products. While the 4-tert-OPnEO provides the same technical functions within all impacted assays, slight variations in the surfactant type provide for intentional differences in assay performance. The selection of surfactant type for different assay products is historically based on slight variations in the ethoxylate chain lengths. a [redacted]. Such variation means that a single surfactant will not be sufficient to act as an alternative in all the impacted products therefore assessments were conducted on two variations of the primary alternative surfactant, alcohol ethoxylated surfactants (1a & 1b) in order to find the most suitable alternative for each of the impacted products. These assessments were therefore conducted using a like for like replacement based on the results of the screening exercise.

5.1 ALTERNATIVE No. 1 Secondary Alcohol Ethoxylate (a&b)

5.1.1 Substance identification and properties

Alternative No.1 is an unbranched secondary alcohol ethoxylate, non-ionic surfactant. Uses are reported in consumer and industrial products such as laundry detergents and all-purpose cleaners and in agrichemicals paper and textiles. The substance is described by a supplier as having good wetting and detergency as well as excellent formulation and handling properties [14]. Table 9 provides details on the substance identification and properties.

Table 9: Alternative No.1 substance identification

Substance name	**EC Number**	**CAS Number**
Secondary alcohol ethoxylate	614-295-4/617-534-0	68131-40-8/84133-50-6
IUPAC Names	Structural Formula	Purpose
Alcohols, C11-15-secondary,ethoxylated Alcohols, C12-14, secondary ethoxylated		Multipurpose surfactant
[13] [15]		

Unbranched secondary alcohol ethoxylates have been identified as the most promising potential alternative to the octylphenol ethoxylates, 4-tert-OPnEO in the Applicant's product range. The secondary alcohol ethoxylates have been selected for further analysis as Alternative No. 1 (1a&b). Substance identification of individual alcohol ethoxylates via CAS/EC number is typically based on the alcohol moiety but can also reflect the degree of ethoxylation in some cases. The manufacturer's product literature has used both *Alcohols, secondary C12 -14, ethoxylated* (CAS: 84133-50-6/EC: 617-534-0) and the *Alcohols, secondary C11-15, ethoxylated* (CAS: 68131-40-8/EC: 614-295-4 to identify these surfactants. The Applicant completed mass spectroscopic analysis of 12 unique supplier lots of material finding the alcohol moiety to be mostly C13 with lesser amounts of C12 and C14; C11 and C15 species were not detected.

The surfactants currently used in the product applications require two different octylphenol ethoxylates as their physicochemical properties are influenced by both the hydrophobe moiety (octylphenol, secondary alcohol) as well as the degree of ethoxylation. Within both the octylphenol ethoxylates and the secondary alcohol ethoxylates, these properties vary with the degree of ethoxylation. Since the various applications currently require two octylphenol ethoxylates because of their different surfactant properties, the Applicant has chosen two corresponding secondary alcohol ethoxylates as Alternative No. 1 to achieve the similar effects in their products. Although differing slightly in properties, both are identified by the same CAS/EC numbers (either CAS: 84133-50-6/EC: 617-534-0 or 68131-40-8/EC: 614-295-4); given the mass spectroscopy results, either CAS/EC designation is technically correct.

5.2 Technical Feasibility

For the technical feasibility to be verified for an alternative, the Applicant must complete a thorough assessment through product performance testing and design verification for all its IVD assays currently on the market. For the purpose of this section of the assessment, a representative number of tests have been selected to demonstrate how the Applicant plans to confirm technical feasibility of the potential alternatives in each of the impacted assays. Further to identifying potential alternatives, the Applicant commenced a preliminary technical feasibility phase to assess whether the alternative can provide comparative results to the current surfactant when it is used in each of the impacted assays. This phase was necessary to provide a level of assurance that the alternative is capable to proceed to the Design Verification Phase. This phase defines the rate of success with the chosen top alternatives to determine which assays are ready to move to the Design Verification Phase or require

additional characterisation and optimisation with the alternative substance or with a potentially different alternative substance.

5.2.1 Product performance feasibility studies:

Each product undergoing substitution must be manufactured using Alternative No. 1 and, in parallel with the current surfactant in use (4-tert-OPnEO). Each product is individually put through a series of studies to evaluate the technical feasibility. A description of the studies required to be performed is provided below. Depending on the product however, some studies may not be applicable. The entire required set of studies is presented below to demonstrate the complexity of assessment that could be applicable to one of the Applicant's products.

1) *Device Master Record Testing*: Internal in-process and final release quality control testing criteria for all manufactured IVDs.

2) *Accelerated Life Testing:* A study designed to assess the stability of the product.

3) *Precision:* A study that evaluates the within laboratory (total) imprecision (within run, between run, and between days) of the IVD test result. An example evaluation/acceptance criterion would be: The assay shall have a total imprecision of less than or equal to X% CV for a positive specimen within the range of 1 - 4 times the cut-off value, which is the medical decision point.

4) *On-board drift*: A study that evaluates the performance of the IVD test kit over time when stored on-board the instrument. Performed for substitution of OPnEO in the microparticle reagent. Surfactant has the potential to influence microparticle dispersal and adherence to the walls of the reagent kit bottle which could affect stability of the test results over the on-board storage period. An example evaluation/acceptance criteria would be: The reagent shall remain on the instrument for a minimum of 30 days with no more than +/- X% shift in test results from baseline for the test kit.

5) *Seroconversion:* A study that verifies the ability of the test kit to detect the onset of infection. A series of patient samples obtained over the course of an infection are tested to determine the point at which the IVD kit can detect the infection. Reagents formulated with the alternate substance must have earlier or equivalent detection in the seroconversion study.

6) *Negative Percentage Agreement:* A study that evaluates the impact of the alternative substance on the specificity of the IVD test kit. An impact or change in the product specificity could lead to false positive results. Results obtained for a sampling of negative patient specimens tested with reagents formulated with the alternative substance are compared to results obtained with a control reagent prepared with the authorised substance. An example acceptance criteria would be: The substituted lot shall have a resolved relative specificity equivalent or better than the Reference Lot or in some cases, the negative % agreement between reference method and substitution method must be greater or equal than X% (depending on the product and the sample size).

7) *Positive Percent Agreement:* A study that evaluates the impact of the alternative substance on the sensitivity of the IVD test kit. An impact or change in the product sensitivity could lead to false negative results. Results obtained for a sampling of positive patient specimens tested

with reagents formulated with the alternative substance are compared to results obtained with a control reagent prepared with the authorised substance. An example acceptance criterion would be: The positive % agreement between reference method and substitution method must be greater or equal than X % (depending on the product and the sample size).

8) *Method Comparison:* A study that evaluates the accuracy (agreement) between the quantitative results obtained by two methods. Method comparison studies verify that results generated by an IVD kit using reagents formulated with the alternative substance agree with results obtained from a control IVD kit using reagents formulated with the authorised substance. An example acceptance criterion would be: The assay shall have a correlation with the reference reagent with a regression slope of X (+/- *0.1*) and a correlation coefficient (*r*) greater than or equal to (*Y*) for samples across the measuring range of the assay.

9) *LoB/D/Q (Limit of Blank/Detection/Quantitation):* A study to evaluate the impact of the alternative substance on the analytical limits of the blank value, the detection limit, and the limit of quantitation of the target analyte. An example acceptance/evaluation criteria would be: The assay reagent insert shall contain the observed Limit of Blank (LoB) of 0.0ng/ml. The assay shall have a Limit of Detection (LoD) of less than or equal to 0.04 ng/mL. The assay shall have a Limit of Quantitation (LoQ) of less than or equal to 0.5 ng/mL.

10) *Analytical Sensitivity:* Similar to the LoB/D/Q, Analytical Sensitivity is a legacy product requirement applicable for some products.

11) *Functional Sensitivity*: Similar to the LoB/D/Q, Functional Sensitivity is a legacy product requirement applicable for some products.

12) *Linearity:* A check that the assay can detect dilutions of analyte with good recovery.

13) *Drop test:* A test to verify that excessive foaming is not observed upon conditions potentially encountered during shipping and handling.

14) *Interfering substances:* A series of studies intended to verify that various endogenous and exogenous substances potentially present in patient specimens do not interfere with the IVD test result.

5.2.2 Conclusions on technical feasibility

Studies performed so far indicate that Alternative No. 1, secondary alcohol ethoxylate, shows promise as a technically feasible alternative to 4-tert-OPnEO in many of the Applicant's IVD products. However, a final determination of technical feasibility cannot yet be established for all products as determination still requires completion of design verification testing, and external clinical evaluation in the case of transfusion products.

If secondary alcohol ethoxylates are not technically feasible in certain products, those products would require further R&D efforts to ensure performance is at the level obtained with 4-tert-OPnEO. The Applicant continues to evaluate technical feasibility through a combination of optimisation of concentrations and evaluation of additional potential alternatives identified through screening.

5.3 Economic Feasibility

In evaluating the economic feasibility of moving from the existing substance to the most likely alternative, the following cost categories have been evaluated by the Applicant:

- R&D costs: Costs to identify, verify and implement the alternative.
- Regulatory costs: Costs to prepare the necessary documentation to receive marketing authorisation for the products containing the alternative. These are considered part of the R&D costs.
- Raw material costs: Cost of the new alternative and of any other additional raw materials that may be required after reformulation of the reagents.
- Production Equipment costs: New alternatives may require purchasing and qualification of additional equipment.

The R&D costs include identifying the alternative, pursuing small scale technical feasibility trials, design verification activities and the implementation costs. As discussed previously, extensive testing is required in order to verify the alternative meets the acceptability specifications for each product. Approximately 200 products are manufactured using the substance and/or contain the substance in the final formulation of one or more of the IVD kit components. In addition, some of the products are required to complete external clinical performance evaluation studies to show the product meets the user needs in a clinical setting. The current estimate for 4-tert-OPnEO substitution from all of the Applicant's IVD reagents is £10-100 million (£f million) over the course of the requested 5.5-year review period (through 4-Jan-2028).

A significant cost included in the total estimate is related to the regulatory submissions. A review of the regulatory requirements for each country in which the Applicant places the products on the market was completed. Each time a submission is required, a fee is associated for each country. The higher risk assays are typically associated with a higher fee.

The difference in raw material costs after reformulation are negligible as current alternatives are similar in cost to the current substance in use. The cost to complete the verification/validation to move to the new raw material make up a large portion of the R&D costs.

Lastly, the same production equipment can be used for the production of the Applicant's products using the alternative. Therefore, little to no impact is anticipated to the process equipment or operation by customers.

Overall investments and resources needed to develop and implement the substitution of 4-tert-OPnEO are currently estimated at £10-100 million (£f million), which includes the Applicant's R&D activities (labour and materials) and the cost to submit the applications for regulatory approval. The substitution effort was initiated because of the EU REACH Regulation. As the GB sales are 1-25% (d) of the Applicant's EU sales, the cost of substitution used for this analysis will be proportional or £1-10 million (£f million).

In this context, the Applicant has designed its substitution and phase out plan through 2027.

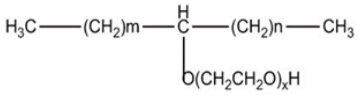
In conclusion, the substitution of 4-tert-OPnEO by the current primary alternative is considered economically feasible for the Applicant over the course of the requested 5.5-year review period (through 4-Jan-2028).

5.4 Reduction of Overall Risk Due to Transition to the Alternative

5.4.1 Substance identification

The Alternative No.1, secondary alcohol ethoxylates, with a chain length of between 11 and 15 carbons as the lipophilic part. Table 10 shows the main identifiers for the Alcohols, secondary C11-15, ethoxylated.

Table 10: Substance identification

Substance Name	Alcohols, secondary C11-15, ethoxylated
CAS Number	68131-40-8
EC Number	614-295-4
Structural formula	
[15],[16]	

Key advantages for transitioning to using alcohols, secondary C11-15, ethoxylated, include the following:

• Not SVHC according to REACH (Regulation (EC) No 1907/2006)
• Not on ECHA CoRAP list of substances
• Not on SIN list by ChemSec
• Not on Swedish Chemicals Agency PRIO database
• Not on Swedish Chemicals Agency Restricted Substances Database

The conclusion is that alcohols, secondary C11-15, ethoxylated does not meet the criteria for being identified as a SVHC according to Article 57 of the REACH Regulation. Transition from 4-tert-OPnEO to Alternative No. 1 would result in a reduction in risk to human health and the environment.

5.4.2 Classification according to Regulation (EC) No. 1272/2008

Table 11: Classification of Alcohols, C11- 15, secondary, ethoxylated

Source	Classification	H-statement(s)	Comments
Harmonised classification	No Harmonised classification	N/A	N/A
Registration	Chronic Aquatic Tox. 3	H412	Eye Damage: conclusive but not sufficient for classification Skin irritation: conclusive but not sufficient for classification Skin sensitisation: conclusive but not sufficient for classification
[15] [17]			

As Table 11 shows, there is no harmonised classification for the substance in Annex VI of the CLP Regulation [17].

An EU REACH registration dossier for CAS No 68131-40-8 associated with the alcohols, secondary C11 – 15 substance has been submitted for the 100-1000 tonnage band [15]. Even though the CAS No is the same, the degree of ethoxylation is different to the proposed substitutes, citing only three ethoxylates in the hydrophilic chain. This is shorter than either of the two products examined as potential Alternative No. 1(a&b) which have ethoxylate chain lengths of approximately 9 and 41 respectively. It has been reported that, for alcohol ethoxylates, aquatic toxicity decreases as the number of ethoxylate units increases [18]. Considering that the carbon chain length remains the same (C11-15), Alternative No. 1 should have lower toxicity than the current registered substance and in turn Alternative 1b would be of lower toxicological concern than Alternative 1a.

5.4.3 Substance status in REACH and CLP Regulations

According to the ECHA data dissemination database [12], there is one registration for the substance with CAS No 68131-40-8, for the 100-1000 tonnes/year tonnage band. It must be noted that the data in the registration dossier are for a secondary alcohol ethoxylate with just three ethoxylate units in the hydrophilic chain. It is used as a representative comparative substance for the substitutes based on the secondary ethoxylate hydrophobic component and the ethoxylate chain acting as hydrophilic component.

Alcohols, secondary C11–15 is not considered a SVHC (i.e. it is not included in ECHA's Candidate List) and is currently not listed in the latest Community Rolling Action Plan (CoRAP) list for substances subject to substance evaluation [19] It is listed on the updated Public Activities Coordination Tool (PACT), list of substance-specific activities including Risk Management Options Analysis RMOA[20].The listing reflects a dossier evaluation activity carried out by ECHA which has concluded and does not impact the classification.

5.4.4 Hazards identification

Overview

4-tert-OPnEO is listed on Annex XIV because of its degradation to octylphenol, which has endocrine disruption properties for the environment. Table 12 compares the hazard classifications of 4-tert-OPnEO, its degradation product octylphenol (OP) and the selected alternative, alcohol ethoxylates.

While the substance is not listed on Annex XIV for human health properties, 4-tert-OPnEO human health hazards are relevant for the uses of the substance by the Applicant and their customers. Comparison and discussion of all hazards are discussed in addition to the environmental classification to show that the proposed alternatives do not pose any additional risk as a result of substitution.

Octylphenol is only relevant for its environmental hazards, as it is expected to only be present in the environment during the waste phase.

Table 12: Comparison of hazard classification of 4-tert-OPnEO, OP and Alternative No.1

	4-tert-OPnEO	**Octylphenol (OP)**	**Secondary alcohol ethoxylates**
EC No / CAS No	618-541-1/9036-19-5 618-344-0/ 9002-93-1	205-426-2 / 140-66-9	614-295-4 / 68131-40-8
Endocrine disruption	ED compound for environment* By degradation to OP	ED compound for environment	None
Physicochemical	None	None	None
Human health	Skin Irritant 2 (H315) Eye Damage 1 (H318) Acute oral toxicity 4 (H302)	Skin Irritant 2 (H315) Eye Damage 1(H318)	Skin Irritant 2 (H315) Eye Damage 1(H318) Acute oral toxicity 4 (H302) Acute inhalation toxicity 4 (H302)
Environmental	Aquatic acute 1 (H400) Aquatic chronic 1 (H410) M factor = 10	Aquatic acute 1 (H400) Aquatic chronic 1 (H410) M factor = 10	Aquatic chronic 3 (H412)
Source(s)	Supplier's SDS [13]	Harmonised classification (Index No: 604-075-00-6)	Supplier's SDS [13] Registration dossier [15]
Notes: *Classification of 4-tert-OPnEO is based on the classification of the degradation product, namely 4-tert-octylphenol (4-tert-OP).			

Endocrine disruption

4-tert-OPnEO was added to the authorisation list because it degrades to octylphenol, which has been shown to be an endocrine disruptor for environmental species.

Secondary alcohol ethoxylates are not endocrine disruptors and their degradation products are not substances with endocrine disrupting properties.

Physicochemical

Alternative No.1 is not classified for physicochemical hazards. The same applies to 4-tert-OPnEO and OP.

Human health

According to a self-classification by the EU supplier, 4-tert-OPnEO causes severe eye damage and has potential for acute toxicity by the oral route.

Conversely, alcohols, secondary ethoxylate products of different ethoxylate chain lengths supplied to the Applicant are not classified for human health hazards. This is based on the result of the chemical safety assessment of substance with CAS Number 68131-40-8 in the registration dossier [15].

According to the registration dossier, the substance is not an acute toxicant, with LD50 above 2000 mg/kg for oral and dermal exposure, with no deaths observed in the respective studies. A review of inhalation toxicity studies with alcohol ethoxylates suggests that acute inhalation toxicity of such substances is low. The substance is also not classified for skin or eye irritation. Furthermore, no systemic hazards (repeated dose toxicity, genotoxicity, reproductive and developmental toxicity, carcinogenicity) were identified by the registrant.

Table 13 presents the Derived No-Effect Levels (DNELs) for the substance in the registration dossier.

Table 13: DNELs of secondary alcohol ethoxylates, according to registration dossier

DNEL	**Endpoint**	**NOAEL**	**DNEL**
Workers Long term systemic effects (inhalation)	Developmental toxicity (oral)	300 mg/kg bw/day	42.32 mg/m^3
Workers Long term systemic effects (dermal)	Developmental toxicity (oral)	300 mg/kg bw/day	6 mg/kg bw/day
General population Long term systemic effects (inhalation)	Developmental toxicity (oral)	300 mg/kg bw/day	21.16 mg/m^3
General population Long term systemic effects (dermal)	Developmental toxicity (oral)	300 mg/kg bw/day	3 mg/kg bw/day
General population Long term systemic effects (oral)	Developmental toxicity (oral)	300 mg/kg bw/day	3 mg/kg bw/day

Environmental

According to the registration dossier [15] corresponding to the CAS Number used, Alternative No. 1 (a&b) have at most an aquatic chronic toxicity 3 classification, which is lower than that of 4-tert-OPnEO and much less severe than OP.

This classification as per the registration dossier for CAS No: 68131-40-8 is based on the substance being readily biodegradable and the results of the aquatic toxicity testing (toxicity to algae and cyanobacteria NOEC = 0.305 mg/l).

Therefore, it can be concluded that the environmental hazard of alternative 1 (a&b) are lower than that of 4-tert-OPnEO and of octylphenol.

- Degradability: The secondary alcohol ethoxylates are readily biodegradable. The manufacturer's safety data sheet [13] indicates > 60% biodegradation during a 28-day test per OECD Test Guideline 301F or equivalent.
- Bioaccumulation: The registration dossier shows that the substance has potential for bioaccumulation, with a calculated Bioconcentration Factor (BCF) between 178 and 3010. Worst case BCF was determined for an 11-15 carbon chain of the alcohol and a single ethoxylate unit. Based on the worst-case value, the registered substance may be considered Bioaccumulative (B), but not very Bioaccumulative (vB).

A QSAR study submitted as part of the registration dossier examining the bioaccumulation also showed inverse relationship between BCF and degree of ethoxylation and between BCF and alcohol carbon chain length. The substance tested in the registration dossier was a C11-15 branched alcohol ethoxylate, with three ethoxylate units. The Alternative No. 1a has an average of 9.5 ethoxylate units, which indicates a much lower BCF than that calculated as worst case above. For Alternative No.1b, which has an ethoxylate chain length of 41, it is expected that the BCF will be even lower.

5.4.5 Conclusion on reduction of overall risk due to transition to the alternative

The major difference between the Alternative No.1 and 4-tert-OPnEO is that alcohols, C11-15-secondary, ethoxylated replaces polyethylene glycol octylphenol ether that is present in the octylphenol ethoxylates. This replacement leads to elimination of the endocrine disrupting properties that are associated with degradation products of octylphenol ethoxylates.

Physicochemical risks are not expected to change, considering that both 4-tert-OPnEO and the alternative have similar properties, and both are not classified for physicochemical hazards.

Human health hazards are expected to be lower for the alternative, considering that it is not classified either for acute or chronic hazards, while 4-tert-OPnEO is classified for acute toxicity 4 and eye irritation. Therefore, there are fewer risks to workers handling the proposed alternative substance.

Finally, the environmental hazards of the alternative are lower, based on the lower chronic aquatic hazard classification and the more favourable environmental fate properties of the alternative. The substance has been classified as chronic aquatic 3 (as opposed to 4-tert-OPnEO acute and chronic aquatic 1 and OP acute and chronic aquatic 1 toxicity classification). Furthermore, due to its structure it is expected to be less bioaccumulative.

As a conclusion, after comparing the hazard profiles of 4-tert-OPnEO and OP to that of Alternative No. 1 the overall risks to human health and the environment after transition to the alternative will be lower.

5.5 Availability

Alternative No. 1 is a commercially available, general-purpose surfactant. It is already in use by the Applicant in a number of its products. Future use of the alternative is not likely to be subject to any

licencing or access rights based on commercial availability. In addition, based on the hazard assessment it does not appear that it will be subjected to any future regulatory risk management that could impact its availability for substitution. The Applicant has already an approved supplier for the surfactant and it has been confirmed that the increased demand for use in reagents can be meet in the substitution timeframe.

In order to complete full technical feasibility assessment, design verification lots must be manufactured in the same facility as the commercial production. Within the Applicant's substitution plan, the design verification lot manufacture is being completed alongside commercial production of IVD reagents therefore there are significant capacity constraints within the manufacturing facility. As such it can be considered a constraint on the availability of the alternative for substitution by the Applicant.

Compliance with global regulations specifically addressing the safety, quality and performance of IVDs is mandatory for all IVD manufacturers. The introduction of any change to the IVDs reagent or test kit is subject to rigorous and lengthy internal quality procedures and external regulatory approval processes. As a consequence, the introduction of any such change requires a multitude of R&D, revalidation activities as well as global regulatory approvals that can accumulate to a worst-case timeframe of 5.5 years from the Sunset Date.

Alternative No. 1 is considered to be commercially available for use in the increased quantities and of quality required for the Applicant to use in its approximately 200 assay products. However, due to the extensive design verification and regulatory approvals process, it will not be possible to complete substitution before the Sunset Date. Therefore, the Alternative is not considered available for complete substitution until after the end of the requested review period.

5.5.1 Conclusion on suitability and availability for Alternative No.1

Suitability

The Applicant has concluded through the screening process that Alternative No.1, (alcohol, ethoxylates 1a & 1b) has properties that most closely match those of 4-tert-OPnEO and therefore, is considered to be the best choice for substitution. The physicochemical properties of Alternative No. 1 are closely aligned with those of the surfactant currently in use therefore it is not anticipated that any changes will be required to be made to the manufacturing process or to the use conditions at customer locations to allow for the substitution. To date a significant number of preliminary technical feasibility studies have demonstrated that Alternative No. 1 (alcohol ethoxylates 1a & 1b) has the potential to act as a suitable alternative in the majority of the Applicant's impacted products. However, final determination of technical feasibility cannot be established until completion of design verification studies planned to be carried out during the requested 5.5-year review period.

Where feasibility studies have demonstrated that Alternative No. 1 cannot act as a potential substitute, plans are in place to assess other shortlisted alternatives from the screening process outlined in section 4. The key substance physicochemical properties of Alternative No. 1 are closely aligned with those of the surfactant currently in use. As such, it is not anticipated that any changes will be required to be made to the manufacturing operating conditions or to the use conditions at customer locations to allow for complete substitution.

With regard to the hazard profile of Alternative No. 1 it is considered to be favourable in comparison to 4-tert-OPnEO as it does not pose a greater risk to the environment with respect to endocrine disrupting properties or to human health.

Availability

Alternative No. 1, secondary alcohol ethoxylates (1a & b), are already in use by the Applicant in a number of its current marketed products. Therefore, the Applicant has already qualified an approved supplier for the surfactants and it has been confirmed that the increased demand for use in its approximately 200 assays can be met within the substitution timeframe. Although the Alternative No. 1 is considered commercially available to the Applicant, real availability for implementation as a substitute is dependent on regulatory approvals of the change. Marketing approval applications must be prepared, submitted and granted by the regulatory authorities in all of the countries where the IVDs are marketed. It is therefore concluded that Alternative No. 1 is not yet available for substitution to the Applicant.

6. OVERALL CONCLUSIONS ON SUITABILITY AND AVAILABILITY OF POSSIBLE ALTERNATIVES FOR USE 1

6.1 Technical Feasibility of Potential Alternatives

A screening process and comparative assessment identified one surfactant type, Alternative No.1, secondary alcohol ethoxylates (two individual surfactants; (1a&b)) (Table 14) as the best option to conduct large scale laboratory trials to investigate the capacity to act as a suitable alternative to 4-tert-OPnEO in the end use of the Applicant's approximately 200 products.

Table 14: Comparative assessment of primary alternative and 4-tert-OPnEO

Original screening ID	Surfactant type	Final ranking	HLB	Surface tension
a	Octylphenol ethoxylate	N/A existing surfactant	13.5	33
1a	Secondary alcohol ethoxylate	1	13.3	30
b	Octylphenol ethoxylate	N/A existing surfactant	17.6	52
1b	Secondary alcohol ethoxylate	1	18.0	45

To achieve a high level of confidence that the alternative will provide comparative technical functionality to the 4-tert-OPnEO, each of the impacted assays manufactured using the alternative surfactant was put through a series of laboratory tests designed to confirm exacting product performance requirements mandated by the Applicant's quality standards and the regulations governing the production and use of IVDs.

Product performance requirements are key criteria used to compare the alternative surfactant to 4-tert-OPnEO in each of the Applicant's impacted assay products. Studies performed so far indicate that the secondary alcohol ethoxylates show promise as a technically feasible alternative to 4-tert-OPnEO in many of the Applicant's IVD products. Preliminary feasibility studies have shown that for seven immunoassay products, secondary alcohol ethoxylates are not technically feasible at this time and will require further R&D efforts as performance with the secondary alcohol ethoxylate was not at the level obtained with 4-tert-OPnEO. The Applicant continues to evaluate technical feasibility for these products through a combination of optimisation of concentrations and evaluation of additional potential alternatives.

While the results presented demonstrate that the primary alternative has the potential to act as suitable alternative for 4-tert-OPnEO in many of the Applicant's reagents, a final determination of technical feasibility cannot be made until completion of all design verification studies. Considering the timeframe to complete all of the design verification, external clinical performance evaluation studies, regulatory submissions and customer conversions phases, it is concluded that the substitution will not be completed before the Sunset Date. The additional time required to complete full substitution in line with the Applicant's R&D, substitution and phase-out plan is 5.5 years beyond the Sunset Date (through 4-Jan-2028).

6.2 Economic Feasibility of Potential Alternatives

The estimated cost arising from the transition to the primary alternative is approximately is £10-100 million (£f million). As the GB sales are 1-25% (d) of the Applicant's EU sales, the cost of substitution used for this analysis will be proportional or £1-10 million (£f million).

The main contributing activities are the extensive R&D costs and regulatory approval costs required for the approximately 200 assay products. The costs of substitution are considered feasible over the course of the requested 5.5 year review period.

6.3 Reduction in Overall Risks from the Use of Possible Alternatives

As part of the screening exercise to identify possible alternatives, the Applicant selected Alternative No. 1, the secondary alcohol ethoxylates owing to its more favourable hazard classification. Furthermore, the complete risk assessment (section 5.4) confirmed the findings of the screening exercise after comparing the hazard profiles of 4-tert-OPnEO and its degradation product (OP) to that of Alternative No.1. The overall risks to human health and the environment after transition to the alternative will be significantly reduced with risks arising from endocrine disruption to the environment being eliminated completely.

6.4 Availability

Alternative No. 1 is a readily available, multi-purpose surfactant. Secondary alcohol ethoxylates are promoted by the manufacturer as suitable alternative to octylphenol ethoxylates from both the cost and performance perspective in a number of applications. The alternative is readily available in the EU in sufficient quantities and the Applicant has already qualified an approved supplier. Although the Alternative No. 1 is considered commercially available to the Applicant, real availability for implementation as a substitute to 4-tert-OPnEO in reagents is dependent on regulatory approval of the substitution across its approximately 200 IVDs.

In order to achieve successful substitution of all of its approximately 200 products, technical feasibility studies must conclude on all assays as well as external clinical studies for some of its assays. Regulatory approvals in all countries where the IVDs are marketed must be obtained. The Applicant must then implement all the necessary changes within the manufacturing process documentation, labelling and instructions to customers. Finally, customers must be allowed the time to complete conversion away from assays containing 4-tert-OPnEO. The additional time required to complete full substitution in line with the Applicant's R&D, substitution and phase-out plan is 5.5 years beyond the Sunset Date (through 4-Jan-2028).

6.5 Overall Conclusion

The Applicant considers that alternative technologies to use of 4-tert-OPnEO in the Applicant's IVD reagents is not a suitable option for finding a potential alternative. As such, the Applicant focused the search on alternative surfactants to 4-tert-OPnEO. One potentially suitable alternative surfactant, identified through literature review and screening activities, was selected for assessment of technical feasibility. The Alternative No. 1 surfactant is commercially available, economically feasible and transition to the alternative would lead to a reduction on overall risk to the environment.

Results to date indicate that the secondary alcohol ethoxylates have the potential to act as suitable alternatives to 4-tert-OPnEO, conclusions on technical feasibility in the final products cannot be made

until completion of design verification studies. Furthermore, the Applicant's substitution schedule entails several phases that are mandated by both internal quality procedures and regulatory requirements that must be completed in a phased manner.

Given the remaining technical feasibility studies to be completed, the external clinical performance evaluation, and the regulatory approval and phase out processes in manufacture and the implementation and conversion at customer sites required, substitution is expected to complete 5.5 years beyond the Sunset Date.

It is therefore not technically possible to substitute 4-tert-OPnEO from the Applicant's reagents and their subsequent use by its customers before the Sunset Date. However, the Applicant is committed to fulfilling its R&D, substitution and phase-out program within the requested 5.5-year review period and supplying its customers with IVD assays that do not contain 4-tert-OPnEO thereafter.

The Applicant requests a review period of 5.5 (through 4-Jan-2028) years to allow for the substitution and phase out of 4-tert-OPnEO in IVD reagents covered under Use 1 (end use of its customers).

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8. APPENDIX I TABLE II (A-D) INSTRUMENTS SYSTEMS OVERVIEW

(a) ARCHITECT Integrated System

The ARCHITECT system is currently the Applicant's most widely distributed system. The modular design of the ARCHITECT family of analysers allows multiple processing modules, which perform all sample processing activities, to be physically joined to form a single workstation or system. The processing module(s) determines the system configuration.

ARCHITECT Systems can be configured to process samples using potentiometric and photometric methods and/or CMIA methods.

Instrument	Market Segment	Test Menu Assays covering tests for Global IVD Classification	Reagents Kits & Components Containing 4-tert OPnEO
ARCHITECT *c*-series	Clinical Chemistry	Clinical Chemistry, Enzymes, Substrates, Electrolytes Reagents, Controls standards and calibrators, Other clinical chemistry, Immuno-chemistry, Specific Proteins, Therapeutic Drug Monitoring, Drugs of Abuse/Toxicology, Rheumatoid-Inflammatory Diseases Markers Cardiac Markers, Controls Standards and Calibrators	Reagents Calibrators
ARCHITECT *i*-series	Immunoassay Core Laboratory	Immuno-chemistry: SARS-CoV-2, Tumour Markers, Thyroid Function Hormones, Fertility/Pregnancy Hormones/Proteins Individual and Specified Hormones/Proteins, Anaemia Related/Vitamin Tests, Therapeutic Drug Monitoring, Auto-Immune Diseases, Cardiac Markers Infectious Diseases- Bacteriology, Hepatitis Viruses, Retroviruses, Other Virology, Parasitology	Reagents Calibrators and Controls Pre-Trigger Solution Trigger Solution

(b) Alinity ci System

The Alinity ci-series, the Applicant's newest system, has a scalable design to provide full integration of clinical chemistry and immunoassay analysis. The Alinity ci-series includes a clinical chemistry module and an immunoassay module, each performing all sample processing activities, and a system control module to provide a single user-friendly interface. Each system can be customised by combining one or more sample processing modules, in multiple configurations, with a system control module to form a single workstation. The Alinity system is a fully automated analyser.			
Instrument	Market Segment	Test Menu Assays covering tests for Global IVD Classification	Reagents Kits & Components Containing 4-tert OPnEO
Alinity c	Clinical Chemistry	Clinical Chemistry, Enzymes, Substrates, Electrolytes Reagents (excluding electrodes) Controls standards and calibrators, Other clinical chemistry, Immuno-chemistry Specific Proteins, Therapeutic Drug Monitoring, Drugs of Abuse/Toxicology Rheumatoid-Inflammatory Diseases Markers, Cardiac Markers, Controls Standards and Calibrators Other Immuno-chemistry	Reagents Calibrators
Alinity i	Immunoassay Core Laboratory	Immuno-chemistry: Tumour Markers, Thyroid Function Hormones, Fertility/Pregnancy Hormones/Proteins, Individual and Specified Hormones/Proteins, Anaemia Related/Vitamin Tests, Therapeutic Drug Monitoring, Auto-Immune Diseases, Cardiac Markers, SARS-CoV-2 Infectious Diseases: Bacteriology, Hepatitis Viruses, Retroviruses, Other Virology, Parasitology	Reagents Calibrators Pre-Trigger Solution Trigger solution

(c) Alinity s System

The Alinity s System is a high-volume, automated, blood-screening analyser that is designed to determine the presence of specific antigens and antibodies by using chemiluminescent microparticle immunoassay (CMIA) detection technology. The system performs high-throughput routine and priority processing that features continuous access and automated retesting. The Alinity s System is intended to produce donor specific and other routine specimen results based on the available menu. It is intended to be used in donor screening, plasma and plasmapheresis screening, and organ donor centres, hospitals, and reference laboratories.

Instrument	Market Segment	Test Menu Assays covering tests for Global IVD Classification	Reagents Kits and Components (containing 4-tert OPnEO)
Alinity s	Transfusion (Blood Screening)	Bacteriology, Hepatitis Viruses, Retrovirus, Other Virology, Parasitology	Reagents Pre-Trigger Solution Trigger solution

(d) ABBOTT PRISM System

ABBOTT PRISM System Overview
The ABBOTT PRISM System is a high-volume, automated immunoassay analyser designed to determine the presence of specific antigens and antibodies by using chemiluminescent immunoassay technology. The system performs batch/continuous access and STAT processing.

Instrument	Market Segment	Test Menu Assays covering tests for Global IVD Classification	Reagents Kits and Components (containing 4-tert OPnEO)
ABBOTT PRISM	Transfusion (Blood Screening)	Hepatitis Viruses, Retrovirus, Parasitology	Reagents